ISSN 0003-2999
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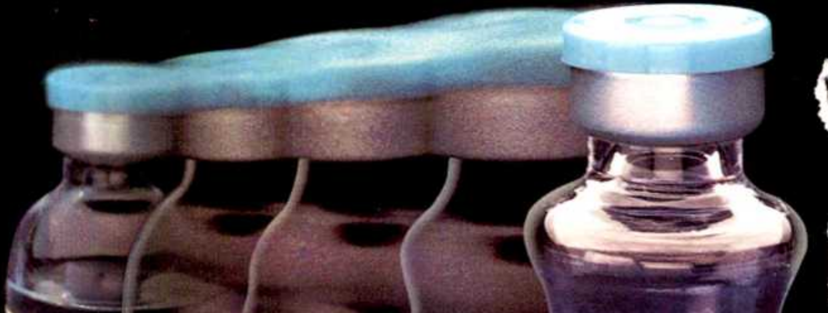

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CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

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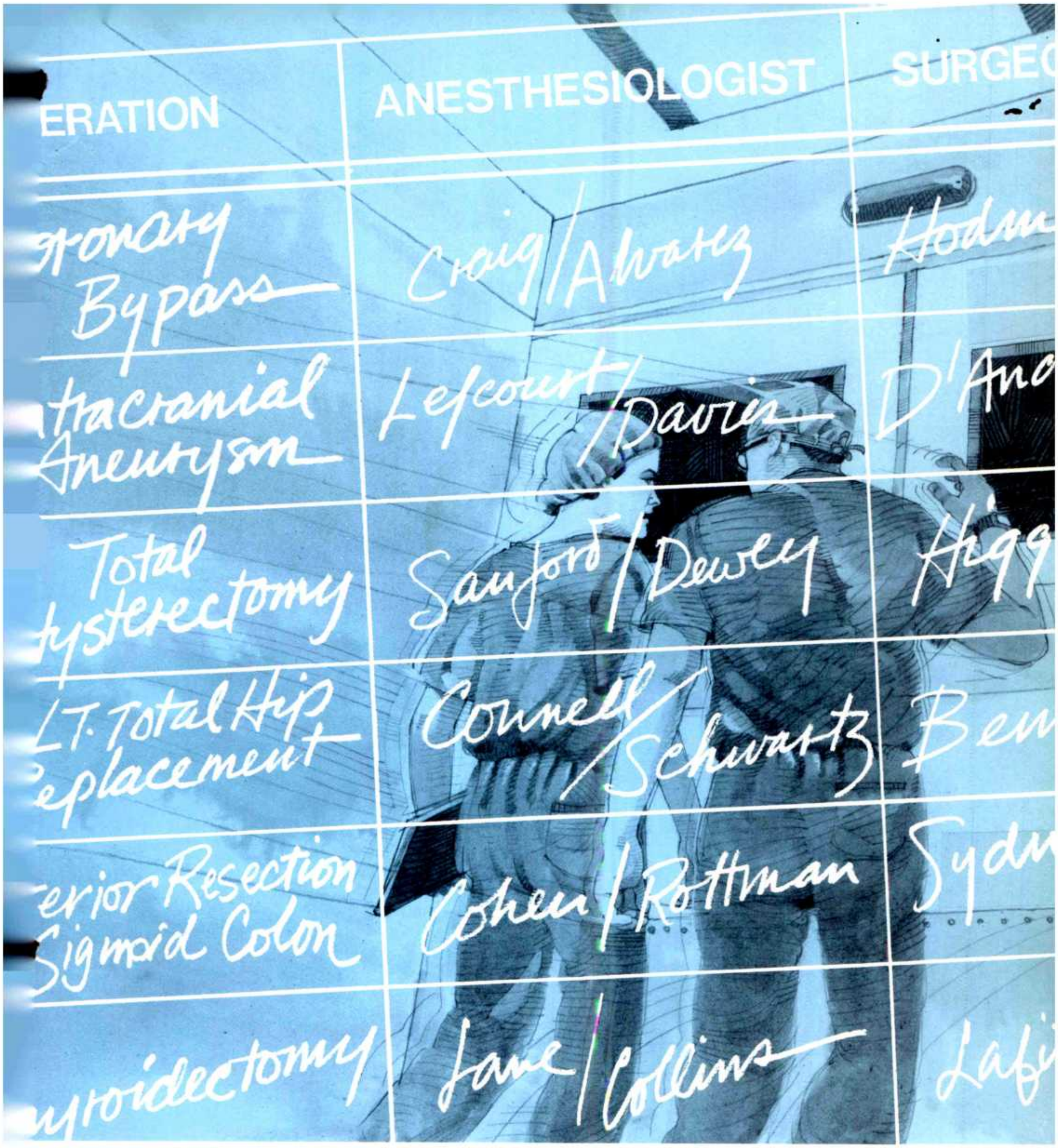
SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 μg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 μg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 μg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all de
of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debil
patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs shou
monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUF
(see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of sk
muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High dos
pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been rep
infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caus
opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respi
depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appro
surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respi
depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative
Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is estab
and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous S
Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be en
when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthe
other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be re
Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SU
should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially c
mised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resis
During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Funct
patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importa
these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA hav
performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intra



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LT. Total Hip eplacement	Connell/Schwartz	Ben
erior Resection Sigmoid Colon	Cohen/Rottman	Syd
yroidectomy	Lane/Collins	Laf

es of SUFENTA as high as 80 μg/kg (approximately 2.5 times the upper human dose) produced no structural mosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic vity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

gnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in es 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due aternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the . No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

or and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such s not recommended.

sing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted man milk, caution should be exercised when SUFENTA is administered to a nursing woman.

atric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular y has been documented in a limited number of cases.

al Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea nd 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times pper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food umption and anoxia, which preclude any meaningful interpretation of the results.

RSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal le rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory ssion and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients istered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). adverse reactions with a reported incidence of less than 1% were: *Cardiovascular:* tachycardia, arrhythmia; *ointestinal:* nausea, vomiting; *Respiratory:* apnea, postoperative respiratory depression, bronchospasm; *Dermatological:* itching, erythema; *Central Nervous System:* chills; *Miscellaneous:* intraoperative muscle movement.

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

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References: 1. Diehl JT, Lester JL, Cosgrove DM: Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg 34* (6):674-679, 1982. **2.** Moggio RA, Rha CC, Somberg ED, et al: Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med 11* (12):943-945, 1983. **3.** Kirklin JK, Lell WA, Kouchoukos NT: Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg 37* (1):40-46, 1984. **4.** Puri VK, Paidipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. *Crit Care Med 9* (12):833-837, 1981. **5.** Shatney CH, Deepika K, Militello PR, et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. *Arch Surg 118*:804-809, 1983. **6.** Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and blood crossmatching. *Transfusion 22* (3):226-228, 1982. **7.** Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med 11*(11):839-850, 1983.

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Usage in Pregnancy: Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.
Usage in Children: No data available pertaining to use in children.
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PRECAUTIONS
The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.
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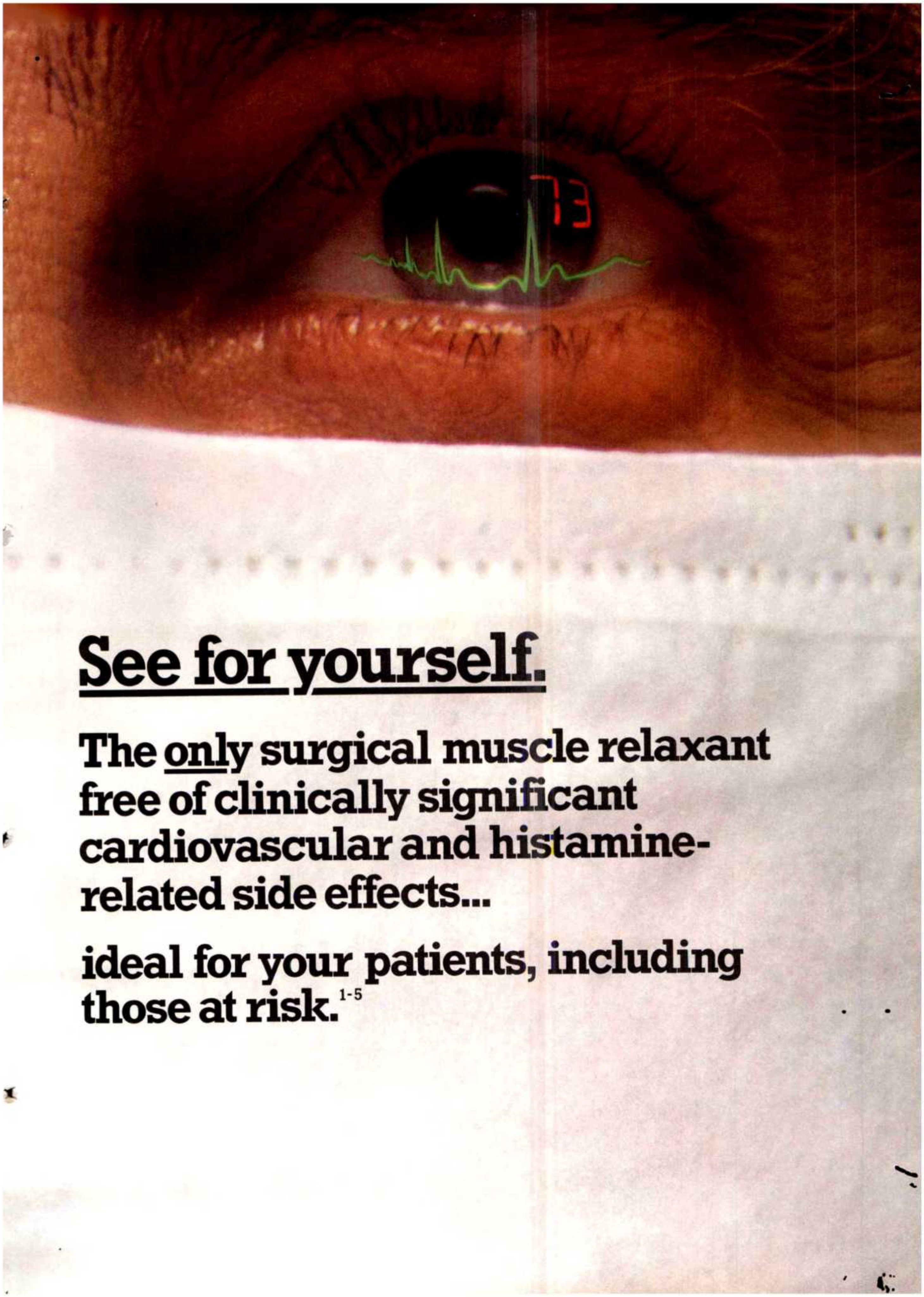

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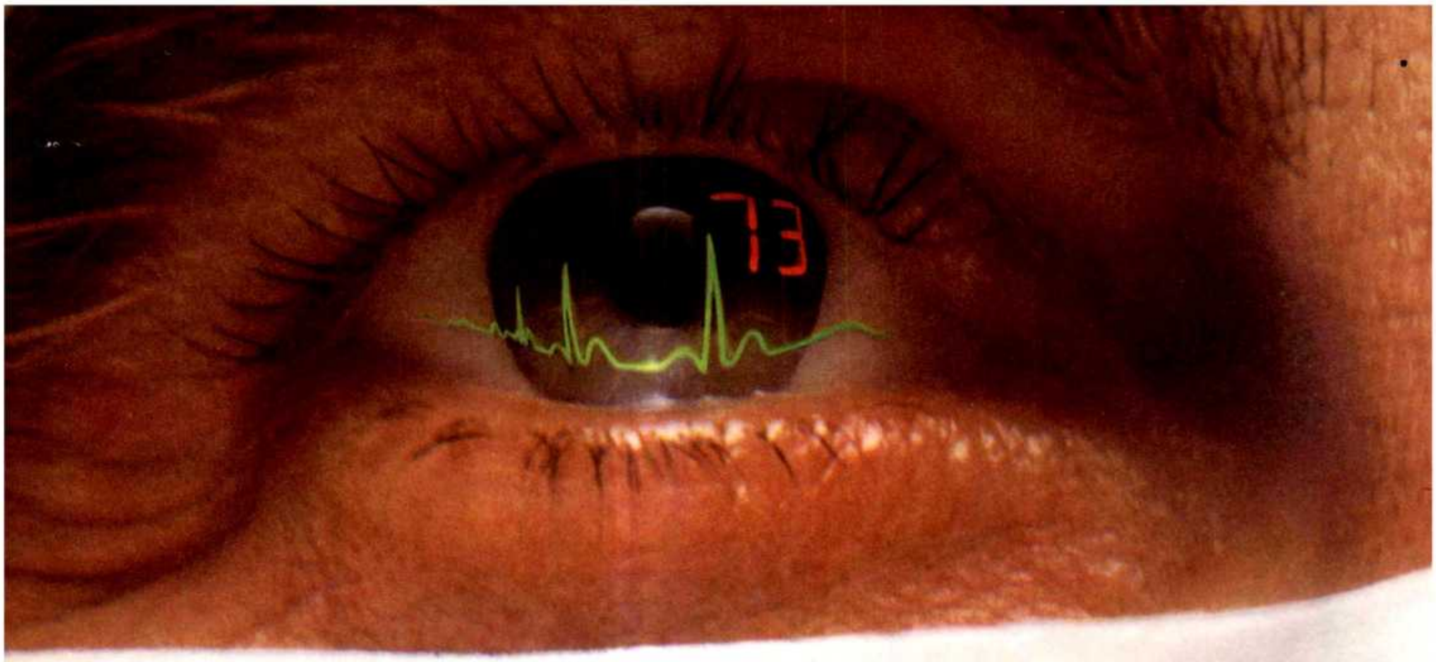

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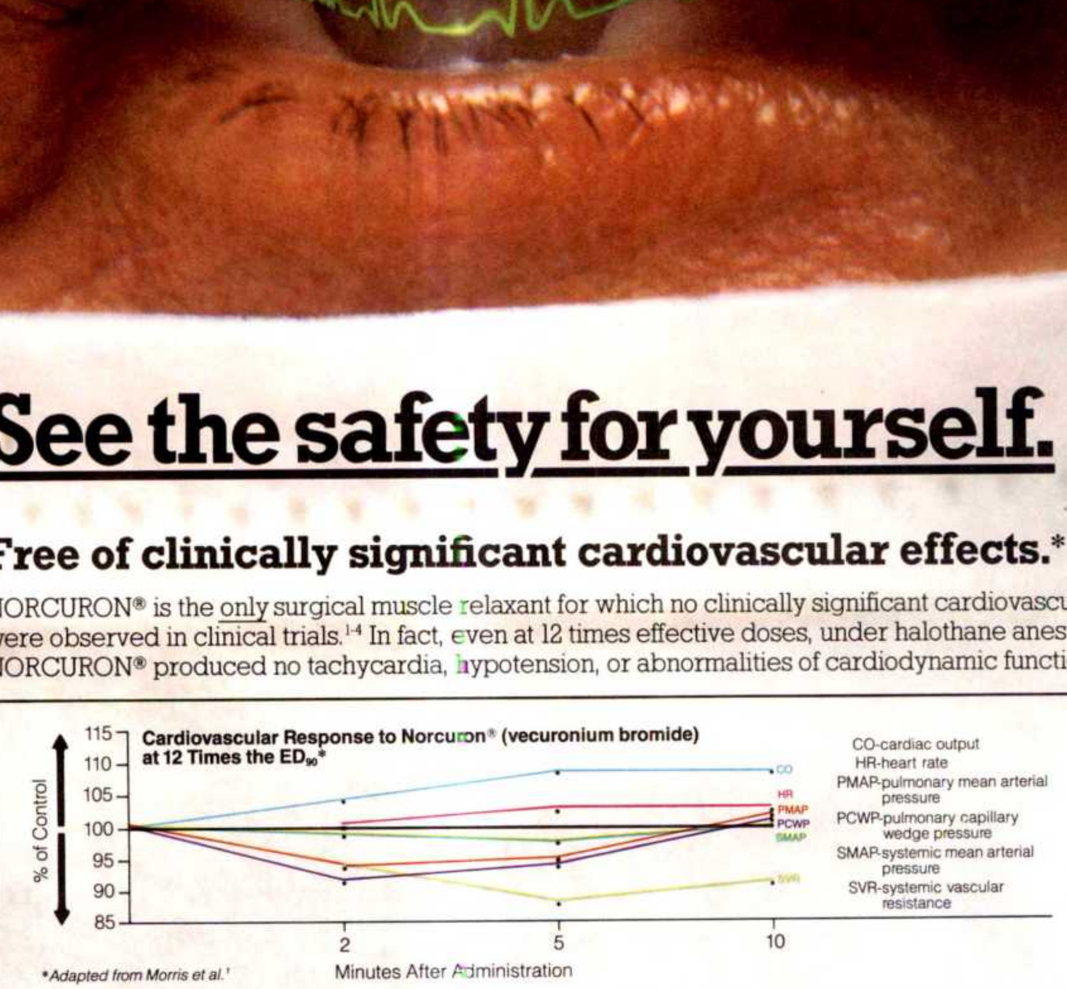

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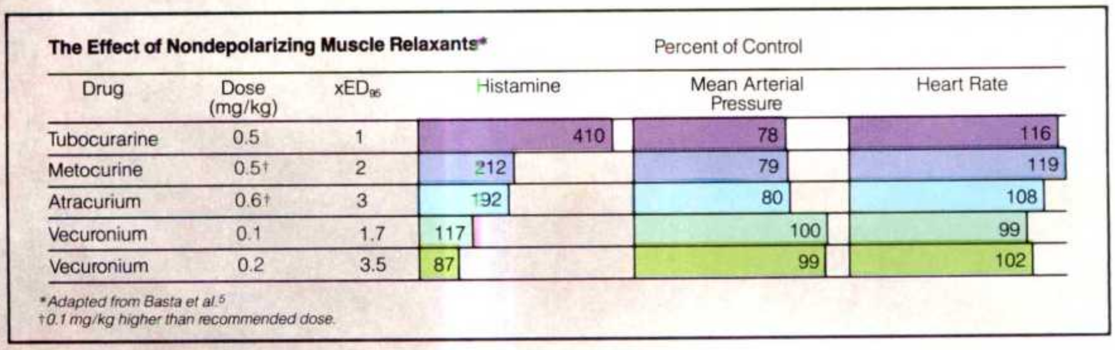
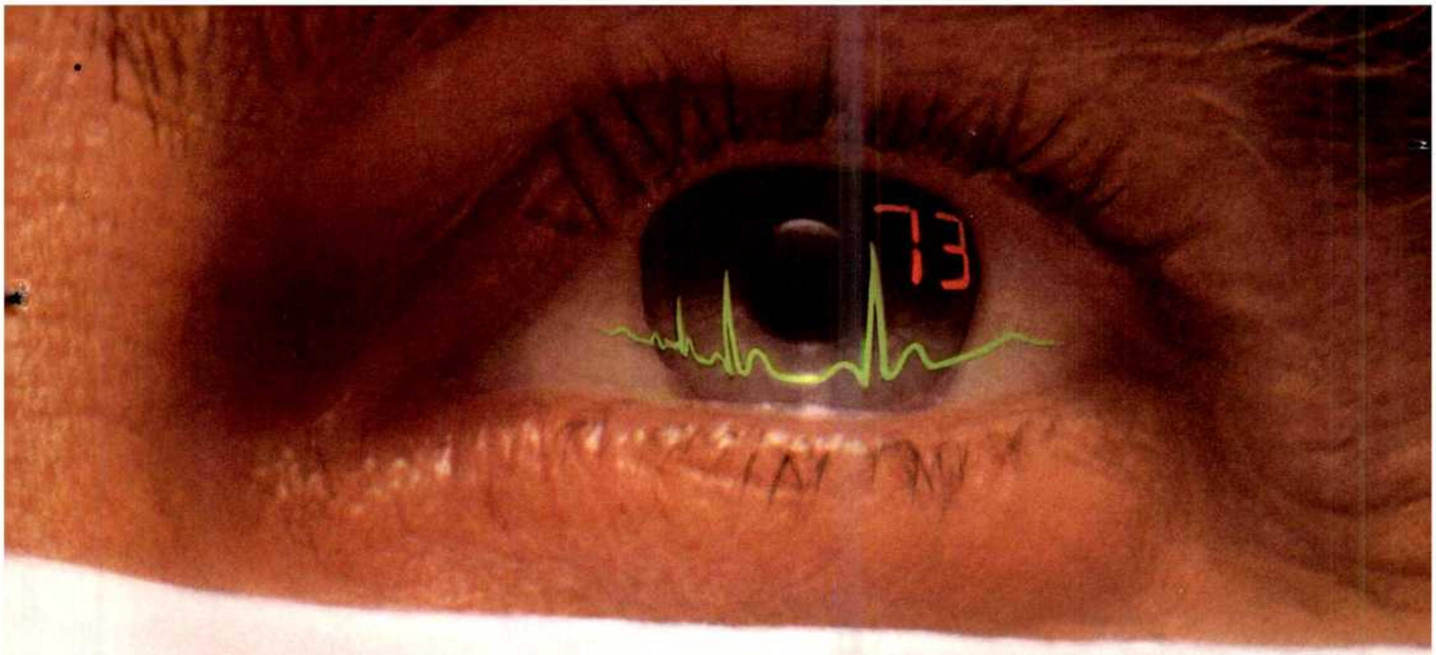


The Effect of Nondepolarizing Muscle Relaxants*

			Percent of Control		
Drug	Dose (mg/kg)	xED_{95}	Histamine	Mean Arterial Pressure	Heart Rate
Tubocurarine	0.5	1	410	78	116
Metocurine	0.5†	2	212	79	119
Atracurium	0.6†	3	192	80	108
Vecuronium	0.1	1.7	117	100	99
Vecuronium	0.2	3.5	87	99	102

*Adapted from Basta et al.[5]

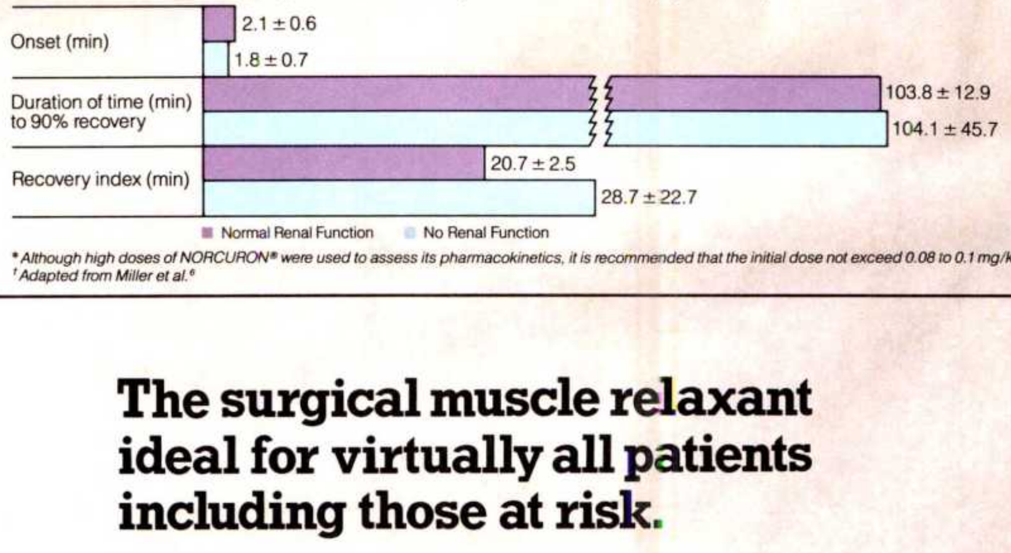
†0.1 mg/kg higher than recommended dose.



Performance unaffected by renal function.[6]

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.[6]

Comparative Indices of Neuromuscular Blockade for Patients With and Without Renal Function Given Equal Doses (0.14 mg/kg)* of NORCURON® (vecuronium bromide) by Bolus Injection†



**Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.08 to 0.1 mg/kg.*
†Adapted from Miller et al.[6]

The surgical muscle relaxant ideal for virtually all patients including those at risk.

Norcuron®
(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. **2.** Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. **3.** Krieg N, Crul JF, Booij LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. **4.** Gallo JA, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. **5.** Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. **6.** Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide).* Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about ⅓ more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

NO REFRIGERATION REQUIRED

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTANT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain theshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
5% glucose in saline
Lactated Ringer's

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 10 (NDC#0052-0442-17).

5 ml vials (contains 10 mg of active ingredient) only. DILUENT (Sterile Water for Injection, USP) NOT SUPPLIED. Boxes of 10 (NDC#0052-0442-57).

STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION. SINGLE USE VIALS.

Manufactured for ORGANON INC. by BEN VENUE LABORATORIES, INC., Bedford, OH 44146 ISSUED 5/86

Organon

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WEST ORANGE, NEW JERSEY 07052

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ORG-8025

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Anesthetic
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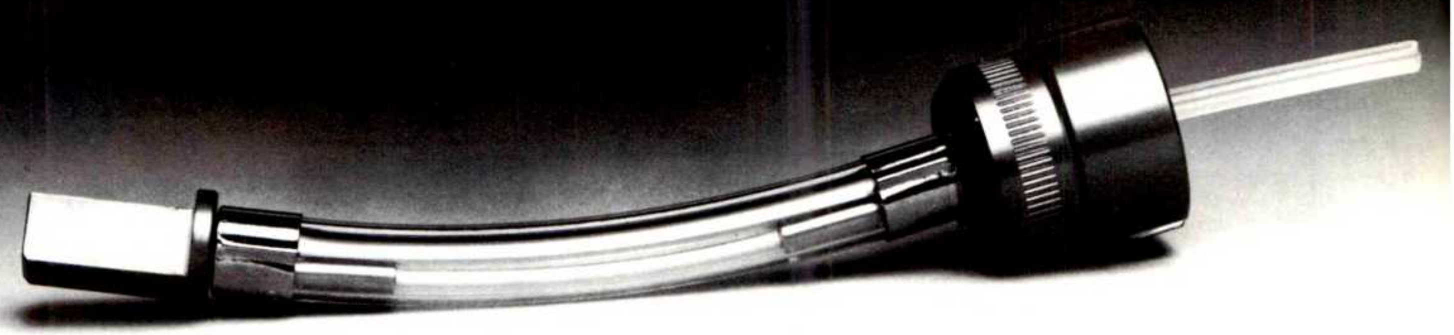
The New Alternative



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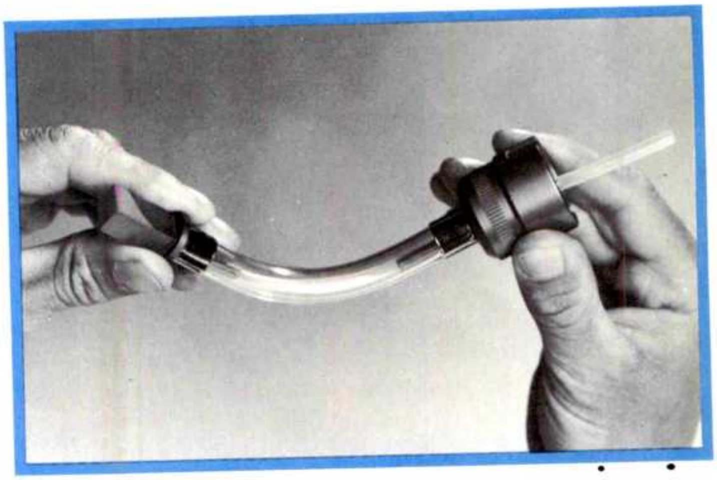

Warranty: All merchandise is guaranteed to be free from defect in material and workmanship for a period of 30 days from the time of delivery.

Manufactured by:

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For outpatient anesthesia

Rapid

Well-suited to the rapid turnover of outpatient cases, the low solubility of isoflurane in blood and tissue (only that of nitrous oxide is lower) enables you to quickly adjust the level of anesthesia to patient and surgical requirements.

Following anesthesia, a rapid washout and prompt recovery provide for your early patient assessment. Patient alertness and cooperation can facilitate handling in the outpatient setting.

Complete

Without *any* other agent or premedicant, isoflurane provides *every* action required for a complete anesthetic, on a closely controlled, breath-by-breath basis: unconsciousness, surgical analgesia, amnesia, and good surgical muscle relaxation—a useful advantage for laparoscopies and orthopedic work, and one that begins when the anesthetic begins and *ends* with elimination of the anesthetic, thereby decreasing the risk of residual paralysis in the PAR.

Because isoflurane is a complete anesthetic when given alone in oxygen or room air, *nitrous oxide can be eliminated* if you choose. Isoflurane anesthetics are seldom complicated and prolonged by postoperative nausea and vomiting.

FORANE® (isoflurane, USP)

Excellent Safety Profile

Stability of heart rhythm and good cardiac output are notable features of an isoflurane anesthetic. CNS excitation does not occur at any concentration or $PaCO_2$ level. Virtually 100% of isoflurane is exhaled unchanged from the patient (only 0.17% of the isoflurane taken up is recovered as metabolites). This near absence of metabolic by-products all but assures an absence of hepatic or renal toxicity from metabolism.

Anaquest

For outpatient anesthesia

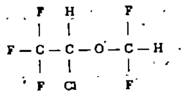
FORANE® (isoflurane, USP)

Rapid...Complete...Excellent Safety Profile

CAUTION: Federal Law Prohibits Dispensing without Prescription.

DESCRIPTION

FORANE (isoflurane, USP) a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$\mathrm{F{-}C(F)(F){-}C(H)(Cl){-}O{-}C(F)(F){-}H}$

Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5 °C (uncorr.)
Refractive index n_D^{20}		1.2990-1.3005
Specific gravity 25 °/25 °C		1.496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \quad \text{where: } A = 8.056,\ B = -1664.58,\ T = {}^\circ C + 273.16\ (\text{Kelvin})$$

Partition coefficients at 37 °C	
Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8
Partition coefficients at 25 °C - rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C	None
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C	Greater than useful concentration in anesthesia.

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY

FORANE (isoflurane, USP) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE

FORANE (isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents.

Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS

General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O.
See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS

Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period. As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;
b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\%\ \text{isoflurane} = \frac{100\, P_V F_V}{F_T (P_A - P_V)}$$

where:
P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (mL/min)
F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED

FORANE (isoflurane, USP), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

A-0336

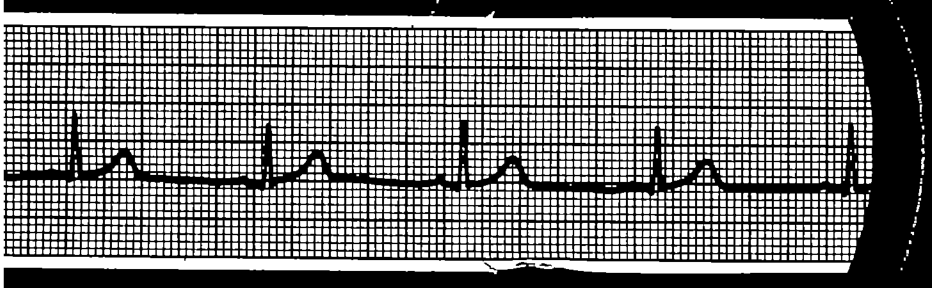
Revised 10-85

Anaquest Forane® (isoflurane, USP)

Anaquest
2005 West Beltline Highway
Madison WI 53713 2318
608 273 0019 . 800 ANA DRUG
A Division of BOC Inc

BOC Health Care

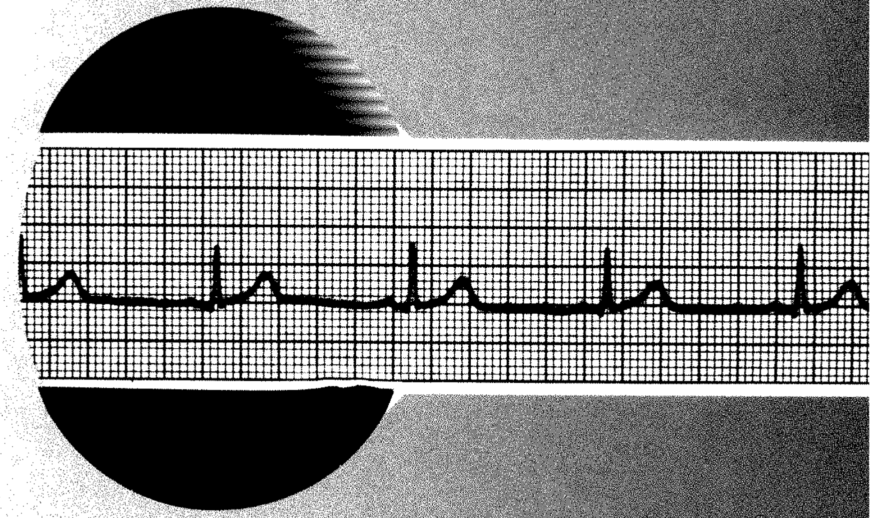
Heart failure patients are often at risk of arrhythmias...



Now... an inotropic agent that does not significantly increase heart rate

energy efficient
Inocor® I.V.
(AMRINONE)

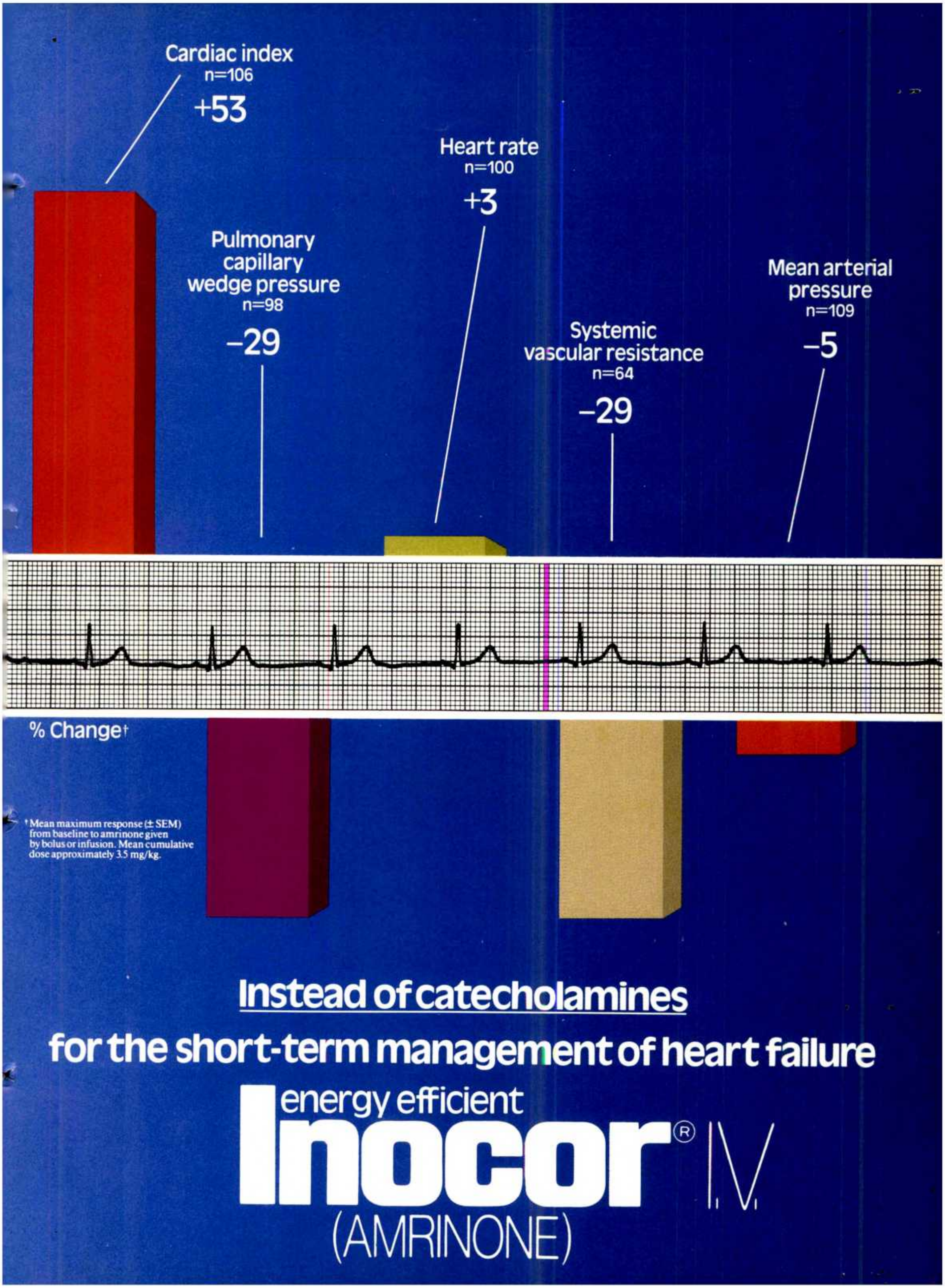
Rapidly increases cardiac output with minimal effect on heart rate or rhythm



- Substantially improves contractility without adding to myocardial oxygen demand
- Lowers pulmonary capillary wedge pressure and systemic vascular resistance
- Heart rate and blood pressure virtually unchanged
- INOCOR is intended for short-term use in patients who can be closely monitored and do not respond adequately to prior treatment with digitalis, diuretics, and/or vasodilators.

*For important product information concerning contraindications, adverse reactions, patient selection, and precautionary recommendations, please see last page.

© 1987 Winthrop Pharmaceuticals



† Mean maximum response (± SEM) from baseline to amrinone given by bolus or infusion. Mean cumulative dose approximately 3.5 mg/kg.

Instead of catecholamines

for the short-term management of heart failure

energy efficient

Inocor® I.V.

(AMRINONE)

A major advance toward better inotropic therapy

energy efficient
Inocor® I.V.
(AMRINONE)

Instead of catecholamines for the short-term management of heart failure

- Independent of the effects of digitalis and catecholamines
- Hemodynamics rapidly improved
- Heart rate and blood pressure not significantly changed... has not been shown to increase risk of arrhythmias (see precautions)
- Can be used in patients with myocardial ischemia
- Benefits sustained during therapy... no evidence of tachyphylaxis
- Easy to administer

Patients receiving INOCOR should be carefully monitored with the following laboratory studies: platelet counts, liver enzymes, fluid and electrolyte changes, and renal function. Hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

Please see brief summary of product information on this page for contraindications, adverse reactions, patient selection, and precautionary recommendations.

Winthrop
PHARMACEUTICALS

Winthrop Pharmaceuticals, Division of Sterling Drug Inc., New York, NY 10016 61066

INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

INDICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-term management of congestive heart failure in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators.)

INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness.

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites.

PRECAUTIONS *General:* INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

LABORATORY TESTS *Fluid and electrolytes:* Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metoprolol, propranolol; hydralazine, prazosin, isosorbide dinitrate, nitroglycerine; chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, potassium supplements, insulin, diazepam.

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace* disopyramide should be undertaken with caution.

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for use in acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been established.

USE IN PREGNANCY *Pregnancy category C:* In New Zealand white rabbits, amrinone has been shown to produce fetal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm this finding. No malformations were seen in rats receiving amrinone intravenously at the maximum dose used, 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN NURSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

ADVERSE REACTIONS *Thrombocytopenia:* Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm³ in 2.4% of patients.

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Cardiovascular effects: Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%).

Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and ascites (one case); myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (one case); and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged, so attribution to amrinone is not certain, but possible hypersensitivity reactions should be considered in any patient maintained for a prolonged period on amrinone.

General: Additional adverse reactions observed in intravenous amrinone clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site of injection (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotension because of its vasodilator effect. If this occurs, amrinone administration should be reduced or discontinued. No specific antidote is known, but general measures for circulatory support should be taken.

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductions:* Asymptomatic platelet count reduction (to less than 150,000/mm³) may be reversed within one week of a decrease in drug dosage. Further, with no change in drug dosage, the count may stabilize at lower than predrug levels without any clinical sequelae. Predrug platelet counts and frequent platelet counts during therapy are recommended to assist in decisions regarding dosage modifications.

Should a platelet count less than 150,000/mm³ occur, the following actions may be considered:

- Maintain total daily dose unchanged, since in some cases counts have either stabilized or returned to pretreatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds the potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were seen infrequently with IV therapy, should severe or debilitating ones occur, the physician may wish to reduce dosage or discontinue the drug based on the usual benefit-to-risk considerations.

Hepatic toxicity: In clinical experience to date with IV administration, hepatotoxicity has rarely been observed. If acute marked alterations in liver enzymes occur together with clinical symptoms, suggesting an idiosyncratic hypersensitivity reaction, amrinone therapy should be promptly discontinued.

If less than marked enzyme alterations occur without clinical symptoms, these nonspecific changes should be evaluated on an individual basis. The clinician may wish to continue amrinone and reduce the dosage or discontinue the drug based on the usual benefit-to-risk considerations.

HOW SUPPLIED Ampuls of 20 mL sterile, clear yellow solution containing INOCOR 5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOCOR lactate equivalent to 5 mg base and 0.25 mg sodium metabisulfite in water for injection.

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

61st CONGRESS - MARCH 14–18, 1987

Buena Vista Palace Hotel, Lake Buena Vista (Orlando), Florida

PRELIMINARY MEETING INFORMATION

PROGRAM / REGISTRATION / HOTEL INFORMATION: Will be mailed in mid-December to all IARS members. (IARS members outside of North America who plan to attend the meeting can receive this material by airmail upon request.) Non-IARS members should request information from the Cleveland Office: 3645 Warrensville Center Road, Cleveland, Ohio 44122. Telephone: (216) 295-1124.

MEETING SCHEDULE: Registration: Saturday, March 14, 1–6 pm (continues daily)
Scientific Program: Sunday, March 15 through Wednesday, March 18
Exhibits: Sunday, March 15 through Tuesday, March 17

SCIENTIFIC PROGRAM

T.H. Seldon Distinguished Lecture:
John W. Severinghaus, MD–"The History of Oximetry"

REVIEW COURSE LECTURES:

Jeffrey L. Apfelbaum, MD
Paul G. Barash, MD
Frederic A. Berry Jr. MD
D. Ryan Cook, MD
Benjamin G. Covino, MD
Edmond I. Eger II. MD
Mieczyslaw Finster, MD
Betty L. Grundy, MD
Patricia A. Kapur, MD
Richard S. Matteo, MD
Richard L. McCammon, MD
Edward D. Miller Jr. MD
Ronald D. Miller, MD
Walter S. Nimmo, MD
Donald S. Prough, MD
J. Gerald Reves, MD
Michael F. Roizen, MD
Paul N. Samuelson, MD
John J. Savarese, MD
Petter A. Steen, MD
Stephen J. Thomas, MD
John H. Tinker, MD
Robert W. Vaughan, MD
Richard B. Weiskopf, MD
Paul F. White, MD

PANEL: *Standards of Care*
Frederick W. Cheney, MD
John H. Eichhorn, MD
Burton S. Epstein, MD
William K. Hamilton, MD
Bruce F. Cullen, MD

PANEL: *Anesthesia Equipment*
John H. Andrews, MD
Forrest W. Fox, MSEE
Betty L. Grundy, MD
A. William Paulsen, PhD
John T. Martin, MD

136 Scientific Papers…55 Scientific Posters…Scientific Exhibits…Theme Luncheons
Board Examinations in Anesthesiology: American Board of Anesthesiology Panel Discussion
Technical (Commercial) Exhibits - Product Seminars: Exhibitor-sponsored morning briefings

REGISTRATION • CME CREDIT • AIR TRAVEL • HOTELS

FEES:	IARS Members	$175 ($200 on site)
	IARS Educational Members	NO FEE
	Non-Members	$350 ($400 on site)
	Non-Member Residents	$50 (with certifying letter)

CME CREDIT: ACCME/AMA: Category 1–31 hours

SPECIAL AIR FARES: United and Delta Airlines, in cooperation with the IARS, will provide reduced rates for round-trip travel to Orlando. Full details will be included in the preliminary program mailing or can be obtained by calling the following numbers (8 AM to 8:30 PM EST daily) and referring to IARS meeting and code numbers shown.
Delta: 1-800-241-6760 – File No. P-0095. *UAL:* 1-800-521-4041 – Acct. No. 7015-H

HOTELS: The Buena Vista Palace and the Royal Village co-host hotel are situated in Walt Disney World Village and provide complimentary bus service to the Magic Kingdom and Epcot Center. Discounted 3- or 4-day passes will be available to IARS registrants and guests. Hotel rates are seasonally competitive, and one rate covers from single to quad occupancy.

Take an esophageal stethoscope, incorporate a Doppler ultrasound probe that monitors aortic blood flow, and you have continuous cardiac output monitoring from Lawrence.

The Lawrence 3000® Continuous Cardiac Output Monitor is your best defense, your greatest patient safeguard, in surgery. It gives you continuous hemodynamic information, allowing faster reaction times and earlier warnings of hemorrhage, myocardial depression or adverse drug reaction.

The Lawrence 3000 continuously monitors cardiac output, cardiac index and systemic vascular resistance. It sets up in minutes. And gives you trouble-free monitoring throughout surgery.

Systemic vascular resistance is based on operator input of BP, or an automatic line transfer from an independent BP monitor.

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Think of it as a
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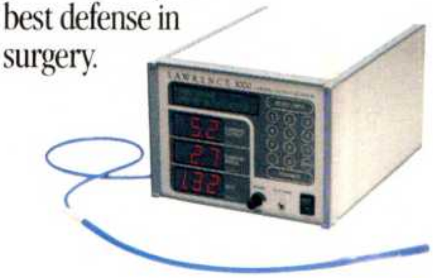
tor comes with in-service training by an experienced professional. Plus instructional videos, clinical studies and operational manuals to help educate your OR staff.

Call Lawrence Medical, Customer Service Department, at 1-800-247-4499 or 1-206-881-1300 (collect in Washington), for a free demonstration, video tape or information package.

Discover how the Lawrence 3000 can be your best defense in surgery.



Continuous cardiac output monitoring from the company who invented it.

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Redmond, Washington 98052
1-800-247-4499
In Washington, call collect:
(206) 881-1300

P24,587

stethoscope that
tors cardiac output.

Artist's conception of the levels of sedation you can achieve with VERSED (midazolam HCl/Roche): 1) preoperative medication, 2) I.V. conscious sedation, 3) induction of anesthesia and as a component of balanced anesthesia.

ROCHE® / DUPONT

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a particular advantage

- **Premedication:**
  virtually painless on injection…
  fast sedative and amnestic action[1]

- **I.V. conscious sedation:**
  superior amnestic effect…
  less tissue irritation[1]

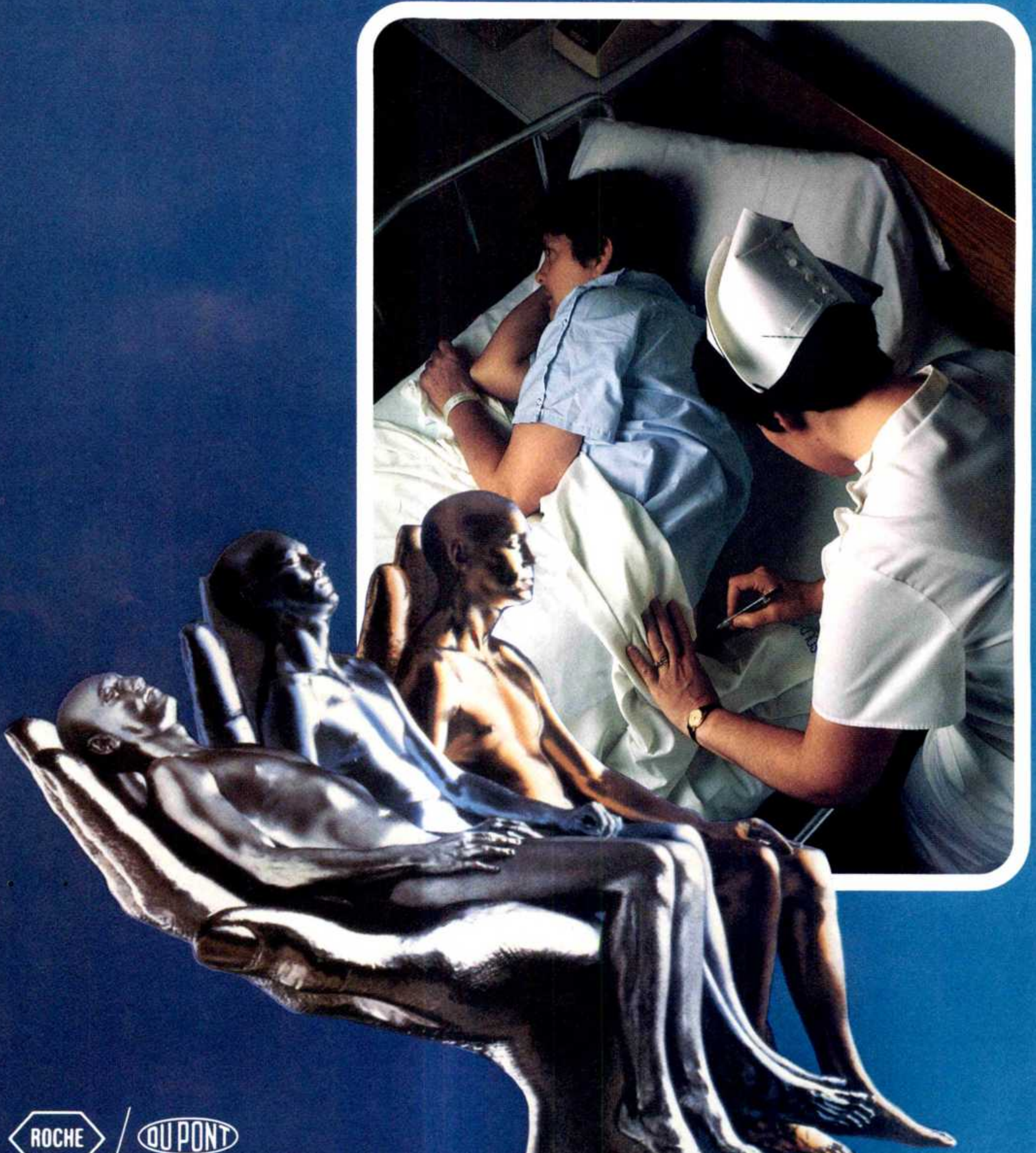
- **Induction and as a component of balanced anesthesia:**
  smooth induction…smooth emergence[1]

INJECTABLE
VERSED®
brand of
midazolam HCl
equivalent to 5 mg/mL
Roche
Ⓒ IV

Please note Dosage and Administration Guidelines and see references and summary of product information on last pages of this advertisement.

The advantage in premedication

Virtually painless faster sedative

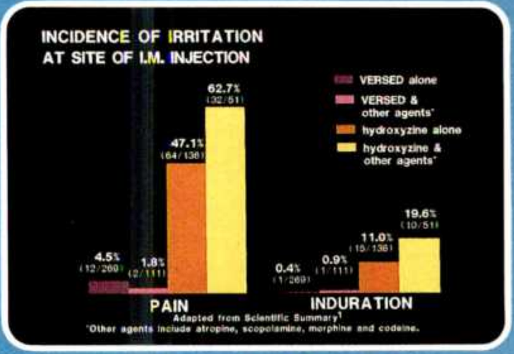


ROCHE / DU PONT

on injection... and amnestic action

Virtually painless

The first stable water-soluble benzodiazepine, VERSED administered intramuscularly produces less pain, induration or tissue irritation than hydroxyzine I.M.[1]



Adapted from Scientific Summary[1]

*Other agents include atropine, scopolamine, morphine and codeine.

Sedates faster

In double-blind premedication studies, onset of sedation was significantly faster and more pronounced with VERSED I.M. than with hydroxyzine I.M. After 15 minutes, 43% of 149 patients treated with VERSED had reached the most desirable levels of sedation compared to only 19% of 101 patients treated with hydroxyzine.[2]

Diminishes recall with a single I.M. injection

Patients treated with VERSED I.M. had significantly less recall of memory cards (7/26) shown during the preanesthetic period than patients treated with hydroxyzine (26/28).[1] Amnesia was greatest 30 to 60 minutes after administration. And when VERSED was given with scopolamine, the period of diminished recall extended to 90 minutes.[1]

Compatible with other agents in the same syringe

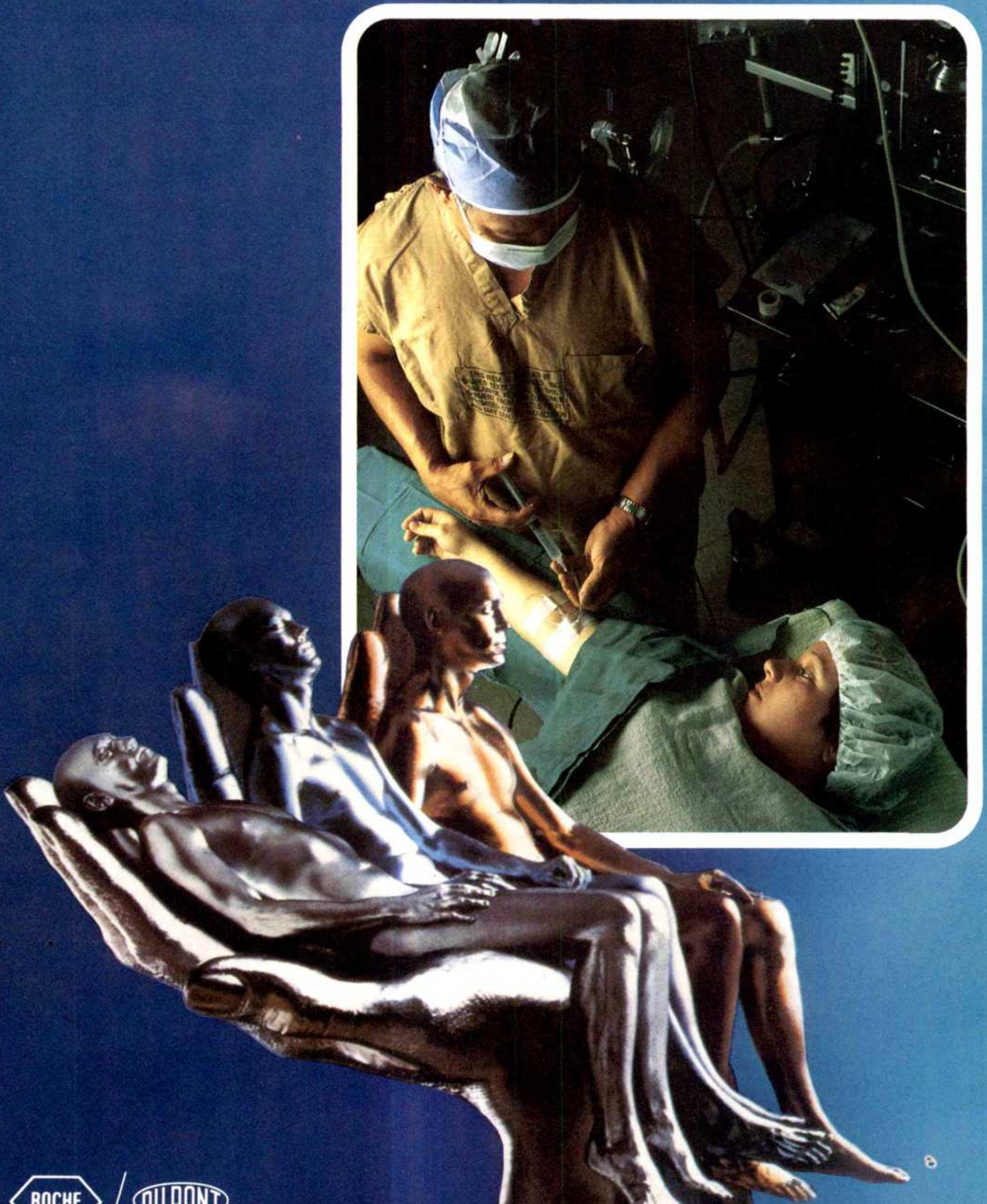
VERSED can be mixed in the same syringe with other frequently used premedicants: morphine sulfate, meperidine, atropine sulfate or scopolamine.

INJECTABLE
VERSED®
brand of midazolam HCl Roche Ⓒ IV

Please note Dosage and Administration Guidelines and see references and summary of product information on last pages of this advertisement.

The advantage in I.V. conscious sedation

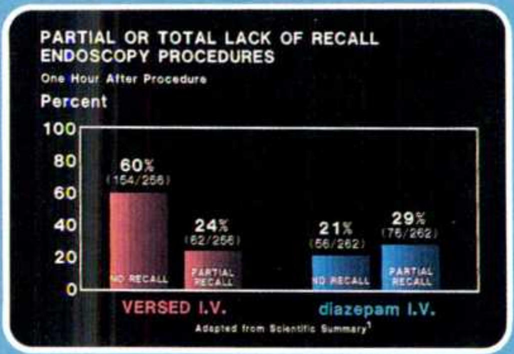
Superior amnestic effect



ROCHE / DUPONT

...less tissue irritation

Significantly less recall



In double-blind, multicenter studies, patients treated with VERSED had significantly less recall of endoscopic procedures than patients receiving diazepam. Of 256 VERSED patients, well over half—60%—had no recall of their procedures when questioned one hour later. By contrast, only 21% of 262 diazepam patients had a similar lack of recall.[1]

Use of a topical anesthetic for peroral procedures and narcotic premedication for bronchoscopies is recommended.

Less irritation

VERSED produced less pain or burning during I.V. administration than diazepam. VERSED also produced less postprocedural irritation: One week following I.V. administration, only 1.4% of 512 patients who received VERSED had tenderness of the vein compared with 3.0% of 503 patients who received diazepam (*P*=0.07).[2]

Faster onset

In the majority of clinical studies, the time required to reach the end point of slurred speech was significantly shorter when patients received VERSED I.V. rather than diazepam I.V. For most procedures, mean time to achieve sedation with VERSED ranged from 2.8 to 4.8 minutes, compared to a range of 2.6 to 9.0 minutes with diazepam.[1]

As a standard precaution, prior to the I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available and a person skilled in maintaining a patent airway and supporting ventilation should be present. Extra care should be observed in the elderly or debilitated (such as lowering dosage by 25% to 30%), and in those with limited pulmonary reserve. Dosage of VERSED should also be lowered by about 25% to 30% if narcotic premedication is used. Caution patients against driving or operating hazardous machinery after receiving VERSED.

INJECTABLE
VERSED®
brand of midazolam HCl
Roche Ⓒⅳ

Please note Dosage and Administration Guidelines and see references and summary of product information on last pages of this advertisement.

The advantage in anesthetic induction and

Smooth induction...

ROCHE / DUPONT

balanced anesthesia

smooth emergence

Smooth induction of anesthesia

Intravenous VERSED provides induction of general anesthesia, prior to administration of other anesthetic agents, as effectively as thiopental in properly premedicated patients.[1] And it does so with significantly less apnea. Among 155 patients who received narcotic premedication and then VERSED, 37% had apnea, compared to 54% of 137 premedicated patients given thiopental.[2]

The initial dose of VERSED I.V. should be given over 20 to 30 seconds and titrated to desired effect. Avoid intra-arterial injection or extravasation. (See Warnings section of summary of product information.)

Dosages of VERSED should be lowered if sedative or narcotic premedication is used.

Minimal adverse hemodynamic effects

While the hemodynamic effects of VERSED I.V. do not differ significantly from those of thiopental, they are somewhat less pronounced.[1] Standard resuscitative equipment should be available, however, and extra care observed in elderly or debilitated patients (such as lowering dosage by 25% to 30%), and in patients with limited pulmonary reserve. VERSED should be administered as an induction agent only by a person trained in anesthesiology.

Valuable as a component of balanced anesthesia for short surgical procedures

VERSED not only works rapidly, it's easily titrated during balanced anesthesia.

Compatible—ready to use

VERSED is compatible with 5% dextrose in water, normal saline and lactated Ringer's solution. No reconstitution or refrigeration is needed. VERSED is available in unit-dose and multidose vials and Tel-E-Ject®
disposable syringes.

INJECTABLE
VERSED®
brand of midazolam HCl Roche (IV)

Please note Dosage and Administration Guidelines and see references and summary of product information on last pages of this advertisement.

Dosage and Administration Guidelines

Indication	Usual Adult Dose	Administration
Premedication	0.07-0.08 mg/kg Approx. 5 mg in the average adult.	I.M., deep in a large muscle mass, approx. one hour before surgery. May be mixed with morphine sulfate, meperidine, atropine or scopolamine.
I.V. Conscious Sedation	2.0-2.5 mg (0.035 mg/kg) (½ mL) for initial titration in average healthy adult. 0.1-0.15 mg/kg is generally adequate as a *total dose*. Up to 0.2 mg/kg may be needed in rare cases, particularly when concomitant narcotics are omitted. Doses in excess of 0.15 mg/kg may result in increased risk of respiratory depression or drowsiness in elderly or debilitated patients. Lower dosage by 25-30% when narcotic premedication is given. Patients over 60 require lower doses—reduce by 30%. Increments of 25% of initial dose to maintain desired level of sedation.	Slow I.V. administration over 2 to 3 minutes; titrate to desired sedative end point, *i.e.*, until the initiation of *slurred speech* is reached. Administer immediately before the procedure. Use of a topical anesthetic for peroral procedures and narcotic premedication for bronchoscopies is recommended. IMPORTANT: Start with the lowest appropriate dose and titrate slowly. VERSED can be diluted with 5% dextrose in water, normal saline or lactated Ringer's solution. NOTE: Potency of VERSED is approximately three to four times that of diazepam.
Induction **As a component of balanced anesthesia for short surgical procedures**	**Premedicated Patients** Range: 0.15-0.35 mg/kg Average adult under 55: 0.25 mg/kg Over 55, ASA I or II: initial dose of 0.2 mg/kg ASA III or IV: 0.15 mg/kg **Unpremedicated Patients** Average adult under 55: 0.3-0.35 mg/kg initially, up to 0.6 mg/kg Over 55: initial dose of 0.3 mg/kg ASA III or IV: initial dose of 0.2-0.25 mg/kg Minimum dose of 0.15 mg/kg Approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary.	I.V. administration over 20-30 seconds. IMPORTANT: Start with the lowest appropriate dose and titrate slowly. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used.

VERSED is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; however, they may be used in patients with open angle glaucoma only if they are receiving appropriate therapy.

Titrate to desired effect

INJECTABLE
VERSED®
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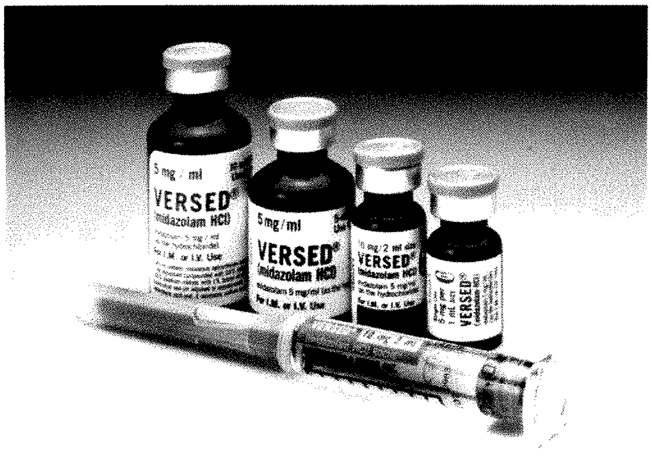

References: 1. VERSED® (brand of midazolam HCl/Roche) Ⓘⓥ, Scientific Summary, Roche Laboratories, Nutley, NJ, 1986. **2.** Data on file (Doc. #069-001,-004,-007), Hoffmann-La Roche Inc., Nutley, NJ.

VERSED® (brand of midazolam HCl/Roche) Ⓘⓥ INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: IM: preoperative sedation; to impair memory of perioperative events. **IV:** conscious sedation prior to short diagnostic or endoscopic procedures, alone or with a narcotic; induction of general anesthesia before administration of other anesthetic agents; as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures (longer procedures have not been studied). When used IV, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: PRIOR TO IV ADMINISTRATION OF VERSED IN ANY DOSE, ENSURE THAT OXYGEN AND RESUSCITATIVE EQUIPMENT FOR MAINTAINING A PATENT AIRWAY AND SUPPORT OF VENTILATION ARE IMMEDIATELY AVAILABLE. IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression; should be administered as induction agent only by a person trained in general anesthesia.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs.

Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Higher risk surgical or debilitated patients require lower dosages for induction of anesthesia, premedicated or not.

Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam. Patients over 55 require lower dosages for induction of anesthesia, premedicated or not. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Increased cough reflex and laryngospasm may occur with peroral endoscopic procedures. Use topical anesthetic and make necessary countermeasures available; use narcotic premedication for bronchoscopy. Decrease intravenous doses by 25% to 30% for elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or circulatory effects noted following administration of succinylcholine.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate:

1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage of VERSED according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular VERSED for premedication.

The use of VERSED as an induction agent may result in a reduction of the inhalation anesthetic requirement during maintenance of anesthesia.

VERSED® (brand of midazolam HCl/Roche) INJECTION

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: The use of injectable VERSED in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.

ADVERSE REACTIONS: Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. These are common occurrences during anesthesia and surgery and are affected by the lightening or deepening of anesthesia, instrumentation, intubation and use of concomitant drugs.

In the conscious sedation studies, hypotension occurred more frequently after IV administration in patients concurrently premedicated with meperidine. During clinical investigations, three cases (0.2%) of transient fall in blood pressure greater than 50% were reported during the induction phase.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, agitation, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, tonic/clonic movements, muscle tremor, involuntary movements, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

DOSAGE AND ADMINISTRATION: Individualize dosage. Elderly and debilitated patients generally require lower doses. Adjust dose of IV VERSED according to type and amount of premedication. *IM use:* Inject deep in large muscle mass. *IV use:* Administer slowly: rapid injection may cause respiratory depression or apnea requiring assisted or controlled ventilation. Administer initial dose over 20 to 30 seconds for induction of general anesthesia. May be mixed in the same syringe with morphine sulfate, meperidine, atropine sulfate or scopolamine. Compatible with 5% dextrose in water, 0.9% sodium chloride and lactated Ringer's solution.

OVERDOSAGE: Overdosage has not been reported, but manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

SUPPLIED: All packages contain midazolam hydrochloride equivalent to 5 mg/mL. Vials: 1 mL (5 mg), 2 mL (10 mg), 5 mL (25 mg), 10 mL (50 mg)—boxes of 10; Tel-E-Ject® disposable syringes; 2 mL (10 mg)—boxes of 10.

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ANESTH ANALG
1987;66:1–8

Does the Duration of Anesthetic Administration Affect the Pharmacokinetics or Metabolism of Inhaled Anesthetics in Humans?

Randall L. Carpenter, MD, Edmond I. Eger II, MD, Brynte H. Johnson, BA,
Jashvant D. Unadkat, PhD, and Lewis B. Sheiner, MD

CARPENTER RL, EGER EI II, JOHNSON BH, UNADKAT JD, SHEINER LB. Does the duration of anesthetic administration affect the pharmacokinetics or metabolism of inhaled anesthetics in humans? Anesth Analg 1987;66:1–8.

To define the effect of anesthetic duration on the pharmacokinetics of inhaled anesthetics, we determined the pharmacokinetics of isoflurane, enflurane, halothane, and methoxyflurane given simultaneously to seven healthy subjects for exactly 30 min and compared the results with data from a previous study in which these four anesthetics were administered for 120 min. End-tidal and mixed-expired anesthetic concentrations were measured during washin of anesthetic and for 3–9 days of washout. Multiexponential (multicompartment) models were fit by least squares to the alveolar washin and washout curves. We estimated the percentage of anesthetic that was metabolized from total uptake and recovery of anesthetic. Alveolar washout was more rapid after the shorter period of anesthetic administration. However, duration of administration did not affect the time constants determined, the number of compartments identified (i.e., five compartments were identified in both studies), or the percentages of anesthetic metabolized.

Key Words: ANESTHETICS, VOLATILE—enflurane, halothane, isoflurane, methoxyflurane, nitrous oxide. PHARMACOKINETICS—kinetics, models, compartments. METABOLISM—drug.

We recently described a noninvasive method for assessing the pharmacokinetic characteristics of inhaled anesthetics in humans (1,2). Four potent inhalational anesthetics (isoflurane, enflurane, halothane, and methoxyflurane) were administered simultaneously for 2 hr at constant inspired concentrations. The alveolar washin and washout of anesthetic and the total uptake and recovery of anesthetic were measured. Pharmacokinetic models were fit to the alveolar washin and washout curves, and the amount of each anesthetic metabolized was derived from the uptake and recovery data.

The present study was designed to assess the pharmacokinetic characteristics of inhaled anesthetics after a much shorter period (30 min) of administration. Comparing the data from the 30-min and 2-hr administrations of anesthetic should provide information on the effect of duration of administration on the following: 1) the rate of the alveolar washout or the position of alveolar washout curves; 2) the time constants determined; 3) the number of pharmacokinetic compartments identified; 4) the relative metabolism of the anesthetics; and 5) the distribution of anesthetics to the tissues. We would expect the following: 1) no effect on washin, but more rapid washout; 2) no effect on the time constants or number of compartments; 3) no effect on the relative rates of metabolism; and 4) distribution should be affected, the more rapidly equilibrating tissues acquiring relatively more anesthetic during a shorter equilibration period.

Methods

We studied seven young (31 ± 4.8 yr old) (mean ± SD) patients, three men and four women, of average height (171.1 ± 6.9 cm) and weight (65.2 ± 7.9 kg). Six patients had donor nephrectomies and one had a colostomy revision; all patients were otherwise healthy. All operations were uneventful. Our study was approved by the Committee on Human Research at the

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Presented at the 1986 IARS Annual Scientific Meeting. This work supported in part by National Institutes of Health grant PO1 AG03014-04.

Received from the Departments of Anesthesia and Medicine, University of California, San Francisco, California, and the Department of Pharmaceutics, University of Washington, Seattle, Washington. Accepted for publication August 20, 1986.

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University of California, San Francisco. Informed consent was obtained from each subject.

All patients were premedicated with morphine and diazepam. Anesthesia was induced with thiopental and fentanyl. Pancuronium or vecuronium was used to facilitate endotracheal intubation and maintain relaxation. Appropriate doses of these agents were given according to the needs of the patients. Patients were ventilated via a nonrebreathing circuit to maintain a normal end-tidal partial pressure of carbon dioxide (36.2 ± 2.3) as measured by mass spectrometry.

After normocapnia was established, the inspired gas was changed from 100% O_2 to 65–70% N_2O, balance O_2. Inspired and end-tidal N_2O concentrations were measured by mass spectrometry. After 30 min of equilibration, the end-tidal partial pressure of N_2O reached 98.0% of the inspired partial pressure. A mixture of potent inhalational anesthetics (isoflurane, 0.365 ± 0.009%; enflurane, 0.568 ± 0.020%; halothane, 0.232 ± 0.009%; and methoxyflurane, 0.0658 ± 0.0085%) was then added to the stream of N_2O delivered to the patients. These constant inspired concentrations were delivered through a nonrebreathing system for exactly 30 min. The average coefficient of variation of the measured inspired concentration in all experiments for all anesthetics was 0.014. To minimize the second gas effect, the inspired concentration of N_2O was decreased by 5% (i.e., to 60–65%) concurrent with the introduction of the potent inhaled agents. After 30 min, the potent inhaled agents were discontinued, and anesthesia maintained for the remainder of the duration of the operation with fentanyl, thiopental, and 60–65% N_2O.

During the 30-min washin period, gas samples were obtained for determination of the fractional concentration of anesthetic inspired (F_I), in the alveoli (F_A), and in mixed-expired gases (F_M). F_I samples were collected proximal to the nonrebreathing valve. F_A samples were collected through a catheter, the tip of which was placed near the tracheal end of the endotracheal tube. The endotracheal tube was connected to the nonrebreathing valve with a length of flexible Teflon® tubing with an internal volume of approximately 100 ml. Teflon® was used to avoid absorption and release of anesthetic that occur with plastics such as polyethylene, and the additional 100 ml of deadspace was used to guard against the contamination of F_A samples with inspired gas. Expired gases were conducted via flexible Teflon® tubing to an aluminum mixing chamber. F_M samples were drawn distal to the aluminum mixing chamber. All gas samples were collected in 50-ml glass syringes and were stored upright (to produce a slight positive pressure) until analyzed.

The F_A samples were collected during washin with each of the first five breaths after the start of administration for six of the seven patients and at 0.25 and 0.5 min for the seventh patient. F_A samples were then collected at 0.75, 1, 1.5, 2, and 3 min. F_A, F_M, and F_I samples were collected at 5, 7, 10, 15, 20, and 30 min. F_I samples were not collected during the first 3 min for logistical reasons. Instead, the F_I values measured at 10, 15, and 20 min were averaged and this value was used as the F_I for the first 3 min. Adequate F_M samples could not be obtained during the first 3 min due to delayed washin of the mixing chamber. Values for F_M during this interval were estimated by the following formula:

$$F_M = f_A \cdot F_A + f_D \cdot F_I$$

Where f_A equals the fractional alveolar ventilation and f_D equals the fractional dead space ventilation. f_A and f_D are the average values calculated from the 10, 15, and 20 min samples using this same formula (i.e., substitute $1 - f_A$ for f_D and solve for f_A, and substitute $1 - f_D$ for f_A and solve for f_D).

During washout (i.e., after administration of the anesthetic vapors was discontinued) we drew F_A and F_M samples at the same intervals as drawn during the 30 min of washin. Samples were drawn thereafter at approximately 40, 50, 60, 75, 90, 105, 120, 150, 200, 350, 500, 700, 1200, 1800, and 2700 min and then once a day for a total of 3–7 days. Minute ventilation ($\dot{V}_E$) was measured concurrently with the above samples using a water seal spirometer. To ensure that the inspired concentration of the four anesthetics was zero, the delivery tubing was changed at the start of washout. Similarly, samples taken after the first 2–4 hr of elimination were collected in "fresh" glass syringes that had not been used to draw samples at the higher, anesthetizing, concentrations. The sampling protocol was interrupted during washout by the end of surgery and extubation. Gas samples were not collected after extubation until the patients were awake enough to be cooperative, and samples were then collected through a mouthpiece and a low resistance nonrebreathing valve. Noseclips were used to prevent breathing through the nose.

To separate and detect isoflurane, enflurane, halothane, and methoxyflurane, we used a two column gas chromatograph (Tracor Model 550). Each column was composed of 10% SF 96 on Chromasorb WHP, 68/80-mesh, 0.32 cm by 6.1 m. Nitrogen carrier was delivered at 45 ml/min through the column to a flame ionization detector at 200°C, which was supplied by hydrogen at 40 ml/min and air at 280 ml/min. One column was maintained at 30°C and was used to separate isoflurane, enflurane, and halothane whose retention times were 3, 3.5, and 5 min, respectively. The second column was kept at 65–70°C and was used to separate methoxyflurane from the other anesthetics. Results were recorded separately on a dual channel strip recorder. Peak heights were proportional to concentration over the entire range of concentrations studied. Calibration standards prepared as described previously (3), were injected at intervals during each study.

The ratio of F_A to F_I (F_A/F_I) was used to define the washin of anesthetic. The ratio of F_A to F_{AO} (F_A/F_{AO}) was used to define the washout of anesthetic. F_{AO} is the alveolar concentration of anesthetic immediately before discontinuation of anesthetic administration.

Multiexponential (multicompartment) models of the form

$$\sum_{i=1}^{n} \frac{A_i}{\lambda i} (1 - e^{-\lambda_i t})$$

and

$$\sum_{i=1}^{n} A_i e^{-\lambda_i t}$$

were fit to the washin and washout data, respectively using least squares analysis (BMDP statistical package, (4)). We fit equations (models) having successively more exponents (interpreted as compartments) to the data for each anesthetic in each patient (i.e., 28 data sets were obtained). For each data set, the model with the greatest number of compartments (highest n) that significantly decreased the residual sum of squares from the model having one less compartment ($n - 1$) was considered to provide the "best fit" ($P < 0.05$, F test) (5).

Time constants were calculated as $1/\lambda_i$ for each compartment. The time constants, for each compartment of the five compartment models, were compared among the anesthetics. The statistical significance of any difference was assessed using paired t-tests with the Bonferroni correction for multiple comparisons (6). The time constants (for each compartment and each anesthetic) were also compared with those determined in the 2-hr anesthetic administration study. The significance of these differences was assessed by unpaired t-tests, again using the Bonferroni correction.

To assess the total uptake of anesthetic and the total elimination of anesthetic by ventilation, uptake and elimination rates were calculated for each anesthetic at each time point. The uptake rates were calculated as $\dot{V}_E \cdot (F_I - F_M)$. The elimination rates were calculated as $\dot{V}_E \cdot F_M$. Total uptake for each anesthetic was estimated as the area under the curve generated by plotting the anesthetic uptake rate against time (trapezoidal method). Total recovery of unchanged anesthetic in exhaled gases (i.e., elimination by ventilation) was calculated by the same method, and the terminal recovery was estimated as the product of the elimination rate at the final time point multiplied by the terminal time constant. The total recovery was divided by the total uptake for each anesthetic, and multiplied by 100 to produce the percentage recovered.

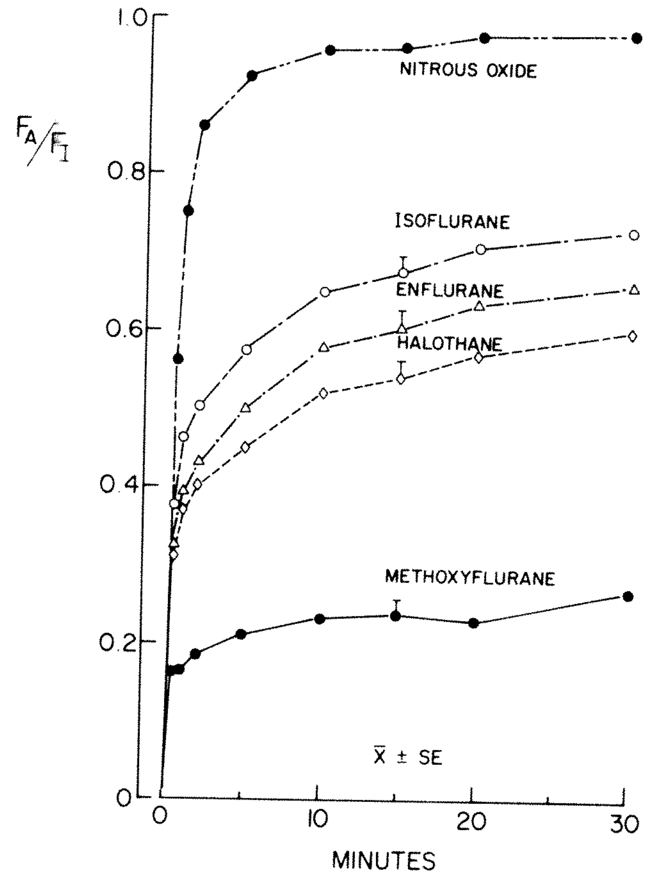

Figure 1. The increase in the ratio of the alveolar to the inspired anesthetic concentration (F_A/F_I) plotted against time ($n = 7$) (Values are mean ± SEM for 15-min points).

To assess metabolism, we first assumed that isoflurane was not metabolized, but that not all isoflurane would be recovered because of loss through the wound or skin and in the urine or feces. We also assumed that these other sources of anesthetic loss would equally decrease the recovery of each anesthetic. To compensate for these losses, the percentage recovery of each anesthetic was normalized to that of isoflurane by dividing the percentage recovery for the anesthetic by the percentage recovery for isoflurane. Deficits in normalized recovery were assumed to be due to metabolism (the normalized metabolism).

Metabolism was also assessed by comparing the total clearances of the anesthetics. Total clearance was calculated by dividing the dose of anesthetic delivered

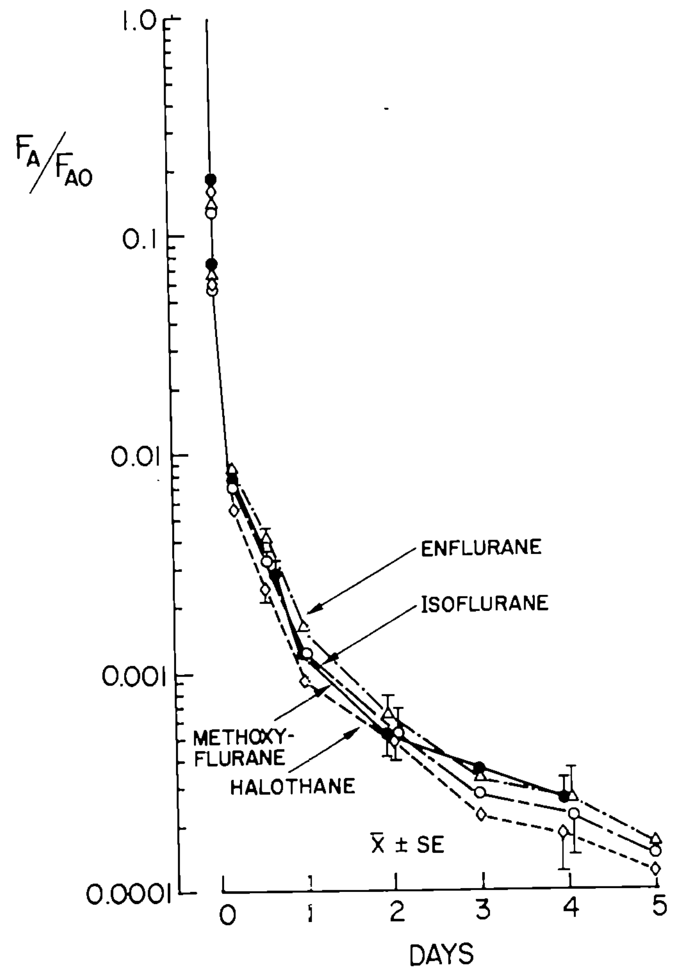

Figure 2. The decline in the alveolar concentration is expressed as a ratio of the alveolar concentration at a given time (F_A) to the alveolar concentration immediately before discontinuation of anesthetic (F_{AO}) and is plotted against time. (Values are mean ± SEM for the 725-min, and the 2- and 4-day time points) (n = 7).

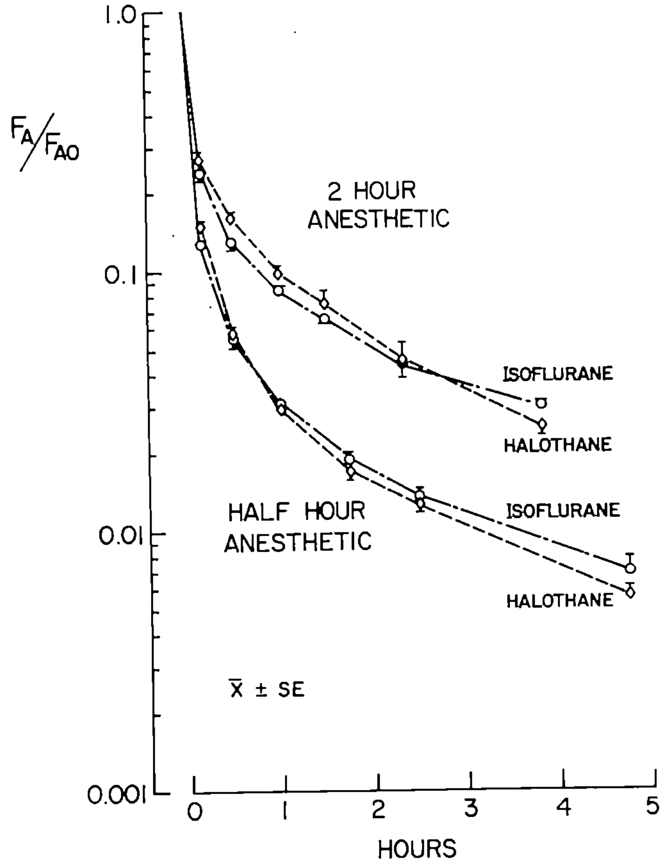

Figure 3. The decline in the alveolar concentration is expressed as a ratio of the alveolar concentration at a given time (F_A) to the alveolar concentration immediately before discontinuation of anesthetic (F_{AO}) and is plotted against time for both the 30-min (n = 7) and 2-hr (n = 9) anesthetic administrations. The F_A/F_{AO} ratio is seen to decrease more rapidly after the shorter anesthetic administration, and the halothane curve is seen to cross the isoflurane curve earlier in the washout. (Values are mean ± SEM).

to the alveoli ($F_I \cdot \dot{V}_A \cdot 30$ min, where $\dot{V}_A = f_A \cdot \dot{V}_E$) by the area under the alveolar washin and washout curves (which was estimated by plotting the alveolar anesthetic concentration against time and calculating the area under the curve using the trapezoidal method). We normalized the clearance of each anesthetic to that of isoflurane using the same assumptions made for the mass balance calculation (i.e., that isoflurane is not metabolized and that it is eliminated only by the lungs or through "other sources of anesthetic loss"). For a given patient, we also assumed that clearances of the four anesthetics by ventilation differed solely as a result of differences in their blood/gas partition coefficients. With these assumptions, the clearance for any anesthetic by factors other than metabolism (largely in exhaled gases) equals the total clearance of isoflurane multiplied by the ratio of the isoflurane blood/gas partition coefficient to the partition coefficient of the other anesthetic. The clearance of anesthetic due to these factors (i.e., other than metabolism) was subtracted from the total clearance, to obtain the residual clearance. Residual clearance divided by total clearance, and multiplied by 100, equals the percentage of anesthetic cleared by metabolism.

The recovery of anesthetic from individual compartments was estimated as:

$$\%\ \text{recovery from compartment } i = (A_i \cdot \lambda_i^{-1}) / \sum_{i=1}^{5} (A_i \cdot \lambda_i^{-1})$$

where A_i and λ_i are the values determined for the five compartments identified by pharmacokinetic analysis of the alveolar washout (of each anesthetic in each patient). The recoveries from each compartment were compared between the anesthetics by paired t-tests

Table 1. Coefficients (A_i) for Washout Data Sets Best Described by Five-Compartment Models

Compartment	Isoflurane ($n = 7$)	Enflurane ($n = 7$)	Halothane ($n = 7$)	Methoxyflurane ($n = 4$)
1	5679 ± 118	5338 ± 174	5420 ± 180	5618 ± 173
2	3155 ± 93	3399 ± 136	3382 ± 198	3269 ± 271
3	666 ± 83	827 ± 98	645 ± 79	656 ± 134
4	99 ± 4	116 ± 5	98 ± 13	96 ± 18
5	17 ± 4	21 ± 5	12 ± 3	19 ± 5

Data are mean ± SEM. All values are multiplied by 10^4.

with the Bonferroni correction for multiple comparisons. We also compared the anesthetic recoveries from each compartment with the recoveries determined for the 2-hr anesthetic administration. The significance of these differences were assessed by unpaired *t*-tests, again with the Bonferroni correction.

Results

The rate of increase in the F_A/F_I ratio was inversely proportional to the solubility of each anesthetic in blood (Fig. 1). In contrast, the rates of decline in the F_A/F_{AO} ratios were not directly proportional to the anesthetic solubilities (Fig. 2). The ratio for halothane decreased below that for enflurane in 19.1 ± 6.0 min (mean ± SEM) and below that for isoflurane in 83.9 ± 34.6 min (Fig. 3). The halothane concentrations at the time of these crossovers were 0.0162 ± 0.0043% and 0.0046 ± 0.001%, respectively. Similarly, the ratio for methoxyflurane decreased below that for enflurane in 122.4 ± 64.8 min, and the methoxyflurane concentration at this time was 0.0008 ± 0.0003%. The terminal rate of decline was linear in all patients.

Alveolar washin data were "best fit" by a two-compartment model for 23 of 28 data sets (four anesthetics in each of the seven patients) and by a three-compartment model for the other five data sets. Although the residual sums of squares of five of the three-compartment models were significantly lower than their respective two-compartment models, these fits were poor due to large coefficients of variation for the third compartment (>100%) or poor separation of the compartments identified (as low as a twofold difference in time constants for adjacent compartments).

The alveolar washout data were "best fit" by a five-compartment model for 25 of the 28 data sets (four anesthetics in each of the seven patients) (Tables 1 and 2). Three sets of methoxyflurane data were incomplete because we could not detect the low concentrations present after only 2–3 days of washout. Because the terminal washout could not be measured, we were unable to accurately identify the terminal compartment for these three data sets and could only fit four-compartment models. A six-compartment model did not provide a better fit for any data set. The maximum mean coefficients of variation of the time constants determined for compartments one through five (i.e., the largest mean coefficient of variation for any one of the four anesthetics) were 0.26, 0.14, 0.21, 0.32, and 0.13, respectively. The time constants for all four anesthetics were similar for each compartment (Table 2). None of the time constants determined in this study were significantly different from those determined for the 2-hr anesthetic administration (using the Bonferroni correction for 4 comparisons, we accept $P < 0.0125$ as significant).

Recovery of anesthetic taken up was greatest with isoflurane, less with enflurane, still less with halothane, and least with methoxyflurane (Table 3).

The percentage of anesthetic that was recovered from each compartment was similar for each anesthetic (Table 4). The percent recoveries from the first and second compartments were significantly greater than the recoveries from these compartments after the 2-hr anesthetic administration ($P < 0.001$). Although the average percentage of anesthetic recovered from the fifth compartment in this study was less than after the 2-hr administration, the difference did not reach statistical significance.

Discussion

The rates of rise in the alveolar concentrations of the five anesthetics (F_A/F_I ratios, Fig. 1) did not differ from those we found previously for the first 30 min of anesthesia (1). The separation of the graphs are consistent with the blood/gas partition coefficients of the agents: the enflurane curve was equidistant from the curves for isoflurane and halothane, just as the partition coefficient for enflurane is midway between the partition coefficients for isoflurane and halothane.

In contrast, a faster alveolar washout followed the shorter anesthetic administration (Fig. 3). For example, after 30 min of washout the F_A/F_{AO} ratio for iso-

Table 2. Calculated Time Constants ($1/\lambda_i$) for Five-Compartment Models of Alveolar Washout Compared with Those Predicted Using Current Interpretations of Uptake and Distribution

	Isoflurane ($n = 7$)	Enflurane ($n = 7$)	Halothane ($n = 7$)	Methoxyflurane ($n = 4$)
	Calculated time constants (min)			
Compartment				
1	0.29 ± 0.02[a]	0.25 ± 0.02[a]	0.27 ± 0.01	0.13 ± 0.02[a]
2	6.13 ± 0.41	5.99 ± 0.54	7.41 ± 0.52	8.26 ± 0.44
3	56.2 ± 2.81	57.5 ± 2.74	52.4 ± 4.20	55.8 ± 14.0
4	405 ± 36	433 ± 28	347 ± 53	356 ± 23
5	2037 ± 398	1942 ± 320[a]	2294 ± 458[a]	2353 ± 327
	Predicted time constants (min)			
Pulmonary				
Washout	0.50	0.50	0.50	0.50
VRG	2.69	2.10	3.00	1.48
MG	50.7	36.3	47.7	33.0
FG	2545	2005	3135	2820

Data are mean ± SEM.
Abbreviations: VRG, vessel-rich group; MG, muscle group; FG, fat group.
[a] Significantly different from each other for this compartment ($P < 0.008$).

Table 3. Estimates of Metabolism Based on Mass Balance Data

Anesthetic	Total uptake (ml)	Total recovered (ml)	Recovery (%)	Recovery normalized to isoflurane (%)	Normalized metabolism (%)
Isoflurane	114.1 ± 4.4	116.0 ± 3.8	101.8 ± 1.1	100.0	0[a]
Enflurane	213.4 ± 10.4	193.1 ± 7.6	90.8 ± 2.0	89.2 ± 1.2	10.8 ± 1.2
Halothane	98.5 ± 4.7	58.5 ± 1.9	59.7 ± 1.9	58.6 ± 1.4	41.4 ± 1.4
Methoxyflurane	44.7 ± 6.7	9.7 ± 2.3	20.8 ± 1.7	20.4 ± 1.5	79.6 ± 1.5

Values are mean ± SEM for nine patients.
[a] Isoflurane metabolism was defined as zero for this calculation.

flurane averaged 0.055 in this study, as compared to 0.134 after 2 hr of isoflurane administration. These relative results are consistent with observations made for isoflurane in man (7) and predictions made using computer simulation models (8). The faster decline in the alveolar partial pressure is due in largest part to the lesser equilibration with anesthetic that occurs during the shorter period of administration, and the resulting greater effect of redistribution during recovery from anesthesia.

The duration of anesthetic administration did not affect the relative positions of the washout curves. The halothane and methoxyflurane curves crossed the enflurane curve (Fig. 2), indicating a more rapid elimination of these two anesthetics despite their greater solubility in blood. The halothane curve also crossed the isoflurane curve. The more rapid decline for halothane and methoxyflurane was also noted in our previous study and was attributed to the metabolism of these anesthetics.

The duration of anesthetic administration did affect the time after anesthesia at which the halothane and methoxyflurane curves crossed those for enflurane and isoflurane. The curves crossed significantly earlier after the shorter anesthetic administration ($P < 0.02$, *t*-test of crossover times). For example, after the half hour administration, the halothane curve crossed the isoflurane curve an average of 84 min into the washout period as compared to 203 min after the longer anesthetic administration. However, the absolute halothane concentrations at the time of crossover (0.0046 ± 0.001% and 0.0047 ± 0.0007%) were the same for both the 30 min and the 2-hr administrations. This finding supports our suggestion (1), that metabolism increasingly affects the elimination of halothane when the halothane partial pressure reaches the K_m (the anesthetic partial pressure at which metabolism occurs at half the maximum rate). Because the F_A/F_{AO} ratios decline more rapidly after a brief anesthesia, a greater effect of metabolism is seen earlier in the washout period. If this interpretation is correct, it suggests that metabolism may play a more important role in the recovery from halothane and methoxyflurane anesthesia after a shorter duration of anesthetic administration.

Duration of anesthetic administration did not affect

Table 4. Percent of Total Anesthetic Recovery Attributed to Each of the Five Compartments for This Study (30-min Administration) and the Previous Study (2-hr Administration)

Anesthetic	Percent/compartment				
	1	2	3	4	5
30-min					
Isoflurane	1.2 ± $0.1^{a,b}$	14.4 ± $1.2^{a,b}$	27.2 ± 3.3	30.1 ± 2.7	27.0 ± 5.5^{a}
Enflurane	0.8 ± $0.0^{a,c}$	12.2 ± $1.0^{a,c}$	29.3 ± 3.6	31.4 ± 3.0	26.4 ± 6.1
Halothane	1.2 ± 0.1^{c}	20.5 ± $2.0^{b,c}$	28.1 ± 4.3	27.7 ± 1.1	22.5 ± 5.1
Methoxyflurane	0.6 ± 0.1^{b}	19.4 ± 3.8	26.3 ± 4.7	22.7 ± 3.4	31.1 ± 8.1
2-hr[d]					
Isoflurane	0.3 ± 0.1	5.7 ± 1.1	26.6 ± 1.0	33.7 ± 2.5	33.6 ± 3.2
Enflurane	0.2 ± 0.1	4.8 ± 0.9	25.9 ± 1.3	33.7 ± 2.8	35.4 ± 3.3
Halothane	0.3 ± 0.1	6.7 ± 1.5	36.5 ± 2.0	27.4 ± 1.5	29.1 ± 3.0
Methoxyflurane	0.1 ± 0.0	3.4 ± 0.8	33.7 ± 3.2	31.6 ± 4.7	31.1 ± 4.7

Values are means ± SEM. $n = 7$ for isoflurane, enflurane, and halothane; $n = 4$ for the 30-min methoxyflurane data; and $n = 6$ for the 2-hr methoxyflurane data.

[a,b,c] Pairs of values are significantly different from each other for this compartment ($P < 0.008$).

[d] These results are calculated from data reported in references 1 and 2.

the time constants determined for the five compartments (Table 2). The time constants for the first, second, third, and fifth compartments were consistent with those predicted (using known tissue blood flows and solubilities) for pulmonary washin, the vessel rich group, the muscle group, and the fat group, respectively. Within each compartment, the time constants were comparable among the anesthetics. This finding is consistent with the identity of blood flow to a given compartment and the similarity of the tissue/blood partition coefficients for these anesthetics.

In addition to the four conventional compartments, we found a new compartment that equilibrates at a rate between that predicted for muscle and fat, which we call the fourth compartment (Table 2). Fat becomes the fifth compartment in our model. We previously suggested that red marrow may account for approximately one quarter of the anesthetic distributed to the fourth compartment (1). The other tissue groups that comprise this compartment are not obvious. We have speculated on the composition of the fourth compartment elsewhere (1), and this study does not provide additional information regarding the identity of this compartment.

Duration of anesthesia did not affect the estimates for anesthetic metabolism (Table 3). We expected a slightly greater metabolism for the shorter anesthetic administration because the faster alveolar washout should result in a shorter period above K_m during washout. However, the expected increase in metabolism did not occur, most likely because we administered inspired concentrations that were 3–40% higher than those in the 2-hr administration (higher inspired concentrations decrease the percent of anesthetic metabolized) (3,9).

The rates of metabolism from both our 30-min and our 2-hr studies are consistent with results from other studies that have estimated metabolism from mass-balance (3,10–13). The rates of metabolism from all mass balance studies are higher than the rates estimated from recovery of anesthetic metabolites (10–12). The difference probably reflects the inability of studies using metabolite recovery to account for all metabolites.

Duration of anesthetic administration did alter the distribution of the anesthetics to individual compartments, as indicated by the percent of total recovery attributed to each compartment (Table 4). For the shorter anesthetic administration, a greater percent of anesthetic came from the first (pulmonary washout) and second (vessel rich group) compartments and a smaller percent from the fifth compartment (fat group). This observation is consistent with current notions of uptake and distribution: using the time constants given by our five compartment model, the times required to reach 95% saturation in the five compartments are approximately 1 min, 15–20 min, 2.5–3 hr, 60 hr, and 4–5 days, respectively. The first and second compartments equilibrate in 20 min, and the succeeding anesthetic uptake is by the third, fourth, and fifth compartments. Thus at a given alveolar concentration, the total uptake by the first and second compartments should be the same for the 30-min and 2-hr administrations, but the percent of the total uptake by these two compartments will be smaller for longer anesthetic administrations.

Isoflurane (Forane®) and enflurane (Ethrane®) for this study were donated by Anaquest. Halothane (Fluothane®) was donated by Ayerst Laboratories.

References

1. Carpenter RL, Eger EI II, Johnson BH, Unadkat JD, Sheiner LB. Pharmacokinetics of inhaled anesthetics in humans. Anesth Analg 1986;65:575–82.
2. Carpenter RL, Eger EI II, Johnson BH, Unadkat JD, Sheiner LB. Metabolism of inhaled anesthetics in humans. Anesthesiology 1986;65:201–5.
3. Cahalan MK, Johnson BH, Eger EI II. Relationship of concentrations of halothane and enflurane to their metabolism and elimination in man. Anesthesiology 1981;54:3–8.
4. Dixon WJ, ed. BMDP statistical software 1983. Berkeley: University of California Press, 1983:290–314.
5. Boxenbaum HG, Riegelman S, Elashoff RM. Statistical estimations in pharmacokinetics. J Pharmacokinet Biopharm 1974;2:123–48.
6. Glantz SA. Primer of biostatistics. New York: McGraw-Hill, 1981;87–8.
7. Cromwell TH, Eger EI II, Steven WC, Dolan WM. Forane uptake, excretion, and blood solubility in man. Anesthesiology 1971;35:401–8.
8. Stoelting RK, Eger EI II. The effects of ventilation and anesthetic solubility on recovery from anesthesia. Anesthesiology 1969;30:290–6.
9. Sawyer DC, Eger EI II, Bahlman SH, Cullen BF, Impelman DMK. Concentration dependence of hepatic halothane metabolism. Anesthesiology 1971;34:230–4.
10. Holaday DA, Rudofsky S, Treuhaft PS. The metabolic degradation of methoxyflurane in man. Anesthesiology 1970;33:579–93.
11. Chase RE, Holaday DA, Fiserova-Bergerova V, Saidman LJ, Mack FE. The biotransformation of Ethrane in man. Anesthesiology 1971;35:262–7.
12. Holaday DA, Fiserova-Bergerova V, Latto IP, Zumbiel MA. Resistance of isoflurane to biotransformation in man. Anesthesiology 1975;43:325–32.
13. Rehder K, Forbes J, Alter H, Hessler O, Stier A. Halothane biotransformation in man: a quantitative study. Anesthesiology 1967;28:711–15.

Dependence of Lidocaine Potency on pH and P_{CO_2}

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BOKESCH PM, RAYMOND SA, STRICHARTZ GR. Dependence of lidocaine potency on pH and P_{CO_2}. 1987;66:9–17.

Lidocaine solutions with different concentrations of CO_2, NaOH, and HCl in two buffering systems were applied to frog sciatic nerves. The peak of the compound action potential (AP_c) and the firing threshold for single axons were measured. The amount of lidocaine required at steady state to double the firing threshold of single fibers or to reduce the peak of the AP_c by 40% was used as the index of potency. Acidification with CO_2 increased potency (less lidocaine was needed to achieve either criterion), whereas acidification with HCl diminished potency, as compared with alkaline conditions. These results were true whether or not the perineurium was present. Frequency-dependent block (B_f) increased in acid conditions produced by CO_2, whereas B_f was less under acid conditions produced with HCl ($P < 0.02$). The experiments indicate that CO_2 potentiates conduction block with lidocaine either by a direct effect on the membrane or by its indirect action on intracellular pH, but not from effects on the extracellular pH.

Key Words: ANESTHETICS, LOCAL—lidocaine. CARBON DIOXIDE, TENSION—neural effects.

Initial studies of the neurophysiologic effects of pH did not discriminate among specific acids, bases, or buffers. Thus reduced excitability in acid conditions was reported when P_{CO_2} was varied in the atmosphere surrounding excised nerves (1–3). However, changes in pH produced with other acids or bases had little effect on excitability or conduction velocity (4) or on ionic currents in frog node over the range of pH studied here (pH 6.5–9.00) (5–7). Carbon dioxide is thus not a typical acid and has long been known to decrease excitability of nerves and to stop spontaneous firing in oxygen atmospheres or in solutions depleted of calcium, actions that acidification alone does not duplicate (4,8).

In anesthesia there has been considerable interest in the effects of pH on the potency of tertiary amine local anesthetics, such as lidocaine, that interconvert rapidly between an uncharged free amine base and a cationic protonated form. As the pH increases, this interconversion is biased towards the uncharged species, and lidocaine (pKa 8.2 at 25°C) is thus more permeant through the cell membrane and other lipid diffusion barriers such as the nerve sheath in more alkaline conditions (9–11). The pH also influences the partitioning of anesthetic between aqueous solutions and biologic membranes, which can be expected to have strong effects on the rate of diffusion of anesthetics to the center of a nerve (9,12). There is a consensus that for nerves with intact sheaths, local anesthetics are more potent in alkaline conditions than in neutral or acid conditions (12,13–16). However, acidification with CO_2 has been reported to enhance both rate and potency of local anesthetic action (11,17,18). Evidence from clinical studies concerning the benefits of carbonated lidocaine in epidural anesthesia is contradictory (17,19–21). Blocking action increases reversibly with increases in P_{CO_2} in excised nerves bathed by solutions containing lidocaine, procaine (18,11,22), or bupivacaine (23,24). Investigators have attributed this result to diffusion trapping of the cationic form in pH gradients (23,24) combined with a direct depressant action of CO_2 (18,22).

At steady state, potency depends, in part, on the "local" concentration of anesthetic in the region(s) of the membrane where it acts to block sodium channels. Local concentrations of drug depend on the ratio of neutral and charged form, which vary with pH (12). Presently it is not possible to predict the pH-dependence of blocking action, nor the combined effects of CO_2 and anesthetic on single fibers.

For these reasons we have studied the effects of lidocaine in two different systems in parallel: in a

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Supported by the Burroughs Wellcome Research Fund and USPHS GM30160 and GM35647.

Received from the Department of Anesthesia, Children's Hospital Medical Center, Boston, Massachusetts, and the Department of Anesthesia, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Accepted for publication August 13, 1986.

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desheathed whole sciatic nerve where the peak of the compound action potential was monitored, and in single sciatic fibers remaining within the sheath where the threshold for firing an impulse was measured. Results from both systems corresponded, showing that neither the presence of the sheath, temporal dispersion of the compound action potential, nor failure to attain steady state can account for our major result: that the blocking effect of given concentrations of lidocaine is diminished at steady state by acidification with HCl, but is enhanced by acidification with CO_2.

Materials and Methods

The sciatic nerves of *Rana pipiens* were used for all experiments. For the sucrose gap preparation used to record compound action potential (AP_c), the nerve bundle was desheathed, split in half longitudinally, and mounted in a chamber according to the method first described by Stämpfli (25). The nerve bundle was stimulated with square current pulses at 1.5–2.0 times supramaximal intensity and lasting 0.05 msec. The AP_c was displayed on a storage oscilloscope and photographed. Thus the AP_c amplitude would change if the fibers were blocked, if there was substantial temporal dispersion in the 0.8-cm region exposed to drug, or if individual unit action potentials were reduced in amplitude. The stimulus was applied at a region of the nerve not exposed to drug and was held constant throughout the experiment. Temperature was maintained at 20–22°C. Ionic solutions were perfused constantly through the chamber. Control AP_cs were recorded with the nerve stimulated once per minute at 40 Hz in frog Ringer solution (HEPES solution) (Table 1) or in Boyle–Conway bicarbonate solution (BC-CO_2) (Table 1). The pH of the HEPES solution was adjusted with 1N HCl or 3N NaOH. The pH of the BC-CO_2 was adjusted by varying concentrations of CO_2 mixed with air and oxygen and bubbled through the solutions. The concentration of CO_2 ranged from 0.2% to approximately 10% in these experiments. The pH of all perfusates was monitored continuously using a pH electrode mounted upstream of the nerve chamber. Only the bathing solution pH (pH_o) was measured. Lidocaine solution (100 mM) was prepared from the dried HCl salt (Astra Pharmaceuticals, Worcester, MA), diluted in distilled water, and stored at −20°C. The desired concentration of lidocaine was prepared by diluting the stock solution into frog Ringer solution or BC-CO_2.

After obtaining AP_cs from nerves in the control solution, the solution was switched to one containing a known concentration of lidocaine in the same buffer and at the same pH as the control solution. The nerve was allowed to equilibrate with the anesthetic until a steady state level of block was reached as determined by identical recordings of the AP_c over 5 min. Measurements of the AP_c were obtained at stimulation frequencies of once per minute and 40 Hz. Tonic block (B_t) was calculated as the percent decrease in amplitude of the AP_c under steady state conditions, which were usually achieved within 15 min, with the nerve stimulated once per minute. Phasic or frequency-dependent block (B_f) was calculated as the additional decrease in amplitude of the AP_c at high-frequency stimulation (40 Hz).

$$B_t\% = \frac{(\textit{control amplitude} - B_t \text{ amplitude with drug})}{\text{control amplitude}} \times 100 \quad (1)$$

$$B_f\% = \frac{(B_t \text{ amplitude} - \text{amplitude at 40 Hz})}{B_t \text{ amplitude}} \times 100 \quad (2)$$

In the HEPES buffered solutions, a fresh nerve bundle was used for each pH tested, even though the AP_c recovered to control amplitude with washout of the drug. Results for B_t and B_f in HEPES buffer were determined from three separate tests at each pH. In the BC-CO_2 buffer solutions, control amplitudes of the AP_c were obtained at pH 6.4, 7.2, and 8.0. The same nerve bundle was then perfused with a BC-CO_2 solution containing lidocaine at pH 7.2 and B_t and B_f were measured at steady state. The pH of the lidocaine-containing solution was then adjusted between 6.4 and 8.6 by varying the CO_2, and measurements of B_t and B_f were repeated. Therefore, in the BC-CO_2 buffer, measurements at B_t and B_f were obtained on the same nerve bundle at more than one pH value for each concentration of lidocaine.

Monitoring threshold permits observations of changes in electrical excitability of single fibers that

Table 1. Composition of Solutions

HEPES Solution (mmol)[a]		Boyle-Conway Bicarbonate Solution (mmol)[b]	
NaCl	114	NaCl	80.5
KCl	2.5	KCl	1.99
$CaCl_2$	2.0	$CaCl_2$	1.7
HEPES	10	$MgSO_4$	1.17
		Na_2SO_4	0.66
		$NaHCO_3$	25.0
		Na_2HPO_4	2.55
		KH_2PO_4	0.52
		Glucose	3.3

[a] pH adjusted with 1N HCl or 3N NaOH.

[b] pH adjusted by P_{CO_2} using mixtures of 0.2–10% CO_2 in air and oxygen.

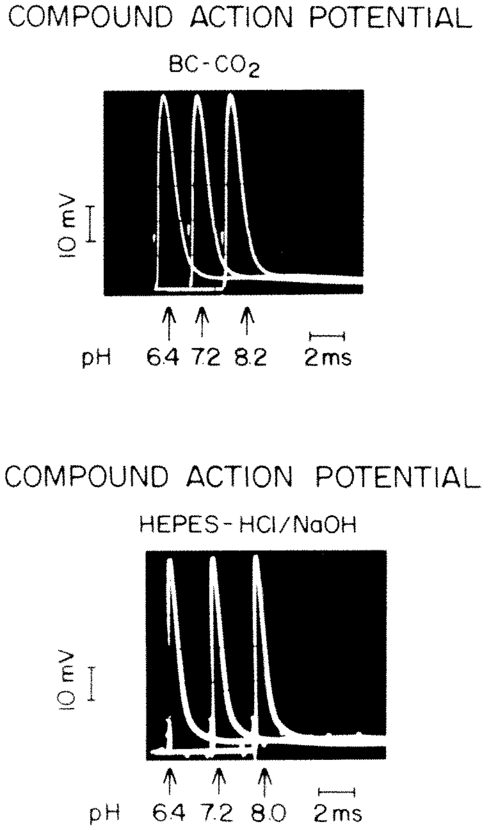

Figure 1. Compound action potentials vs pH in HEPES and BC-CO_2 solutions. Top traces are from nerves in BC-CO_2 solution; bottom traces are from nerves in HEPES solution. Changing the pH with CO_2, NaOH, or HCl had no demonstrable effect on the amplitude of the AP_c, although the AP waveform seemed to be somewhat longer lasting in BC-CO_2 solutions.

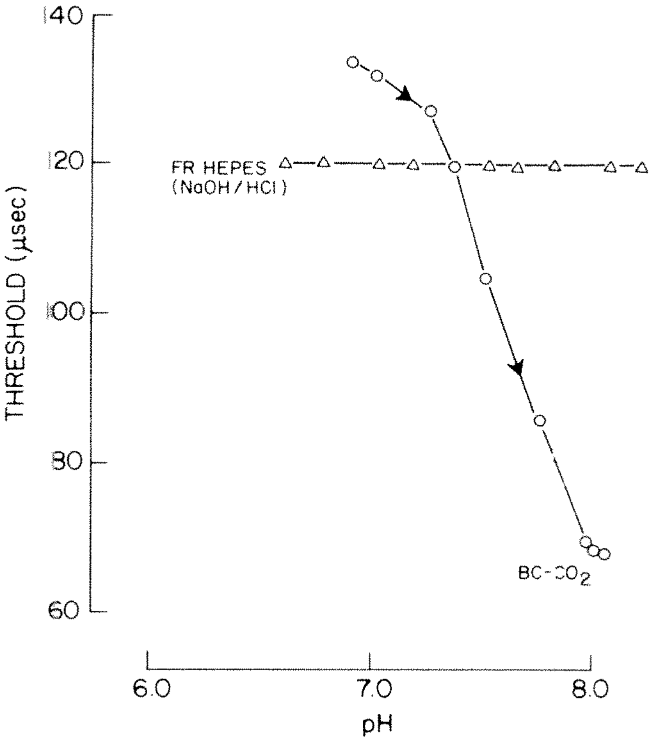

Figure 2. Changes in threshold vs pH in HEPES and BC-CO_2 solutions. In BC-CO_2 solutions, the pH was slowly increased (as shown by the direction of the arrows) by reducing P_{CO_2} in the gas mixture bubbled through the solution. In HEPES solution pH was changed by adding HCl or NaOH. Threshold did not change in HEPES solution between pH 6.6 and 8.0. Threshold changed dramatically in BC-CO_2 solution between pH 6.8 and 8.0.

continue to conduct impulses in the presence of local anesthetic. Both measurements, firing threshold and AP_c height, are influenced by the molecular action of lidocaine. Impulses fail as lidocaine blocks sodium channels, lowering sodium permeability (P_{Na}) and reducing the available current necessary to sustain impulse propagation. Lowering P_{Na} also raises threshold, both in nerve fiber models (26) and in experimental studies of single fibers (27). The effect on threshold can be detected at concentrations well below those needed to block conduction. Here we have used "blocking action" to refer both to impulse blockade and to elevated threshold.

Firing threshold was measured using the threshold hunting technique of Raymond (28). Frog sciatic nerves were excised and the entire trunk was immersed in the solution with its sheath intact. At the distal end, 1 cm of sheath was removed, individual axons were teased from the sciatic nerve bundle, and an action potential from a single fiber was recorded (DC) using Ag/AgCl contacts and suction electrodes. The recording electrodes were located at least 6 cm from the region of stimulation. Threshold was measured by recording the variations required in the duration of current pulses of fixed amplitude to maintain the probability at 50% that an action potential would fire for each stimulus. All experiments were done at 18°C. Resting threshold was recorded by testing the axon every 2 sec throughout each experiment. Lidocaine solutions of known concentration were prepared as described above in frog Ringer solution or in BC-CO_2 and perfused through the nerve preparation. Raw data were plotted as in Figure 3*A* as the threshold (duration in µsec of each test pulse) vs elapsed time. Thus they reflect the sequential changes in the excitability of a single fiber exposed to varying concentrations of lidocaine in solutions at various pH values.

Results

Tonic Effects without Lidocaine Present

Changes in the amplitude of the AP_c were not observed in either the HEPES or the BC-CO_2 solutions in the pH range 6.4–8.0. Figure 1 shows the constant

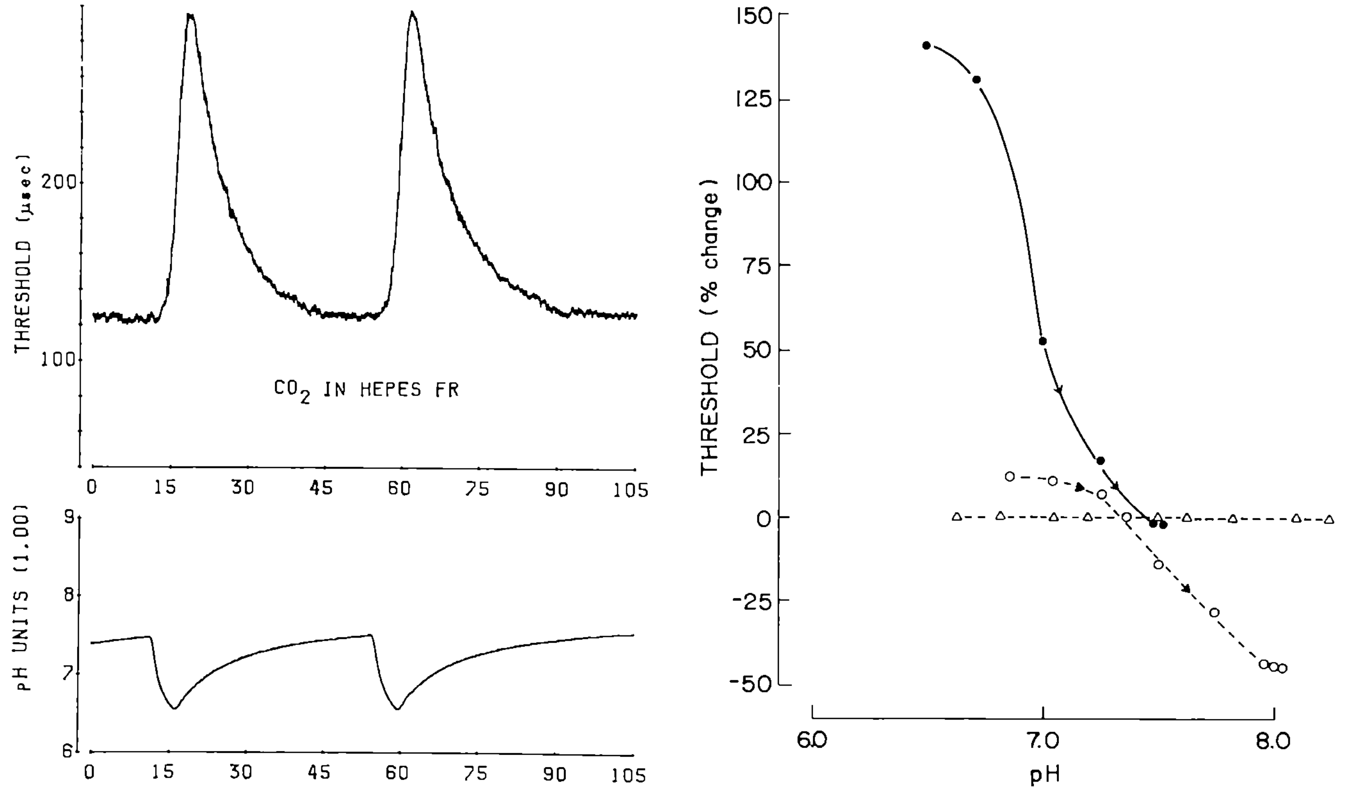

Figure 3. Effects of CO_2 on threshold in HEPES solution. (A) The top curve represents the tracking of threshold in HEPES solution, and the bottom curve indicates the pH recorded upstream from the chamber as it dropped when 5% CO_2 was bubbled through the circulating solution. The abcissa shows elapsed time in minutes. The threshold rose and fell with CO_2. (B) Data from (A) are replotted vs pH. Corresponding points were taken after compensating for the lag between pH measured in the supply stream and the change in threshold of the fiber in the chamber. Although this plot does not represent a steady state relation, comparison with Figure 2 (replotted as dashed lines in Fig. 3B) suggests that the action of CO_2 in HEPES solution is at least as great as in BC-CO_2.

amplitude of the AP_c in both solutions. The conducted impulse has a large margin of safety for conduction (29), and thus the AP_c as measured here will not change amplitude to reveal sub-blocking shifts in excitability. Only actions that had compromised conduction to the point where impulses were dramatically slowed or were blocked in some of the fibers could have been seen; no such large changes occurred.

The effects of changing pH on the resting threshold of the two different buffers are shown in Figure 2. In the pH range 6.8–8.0, resting threshold did not vary in HEPES solution, but it did in BC-CO_2 solution. In the latter, the resting threshold decreased inversely with pH, i.e., was directly related to the concentration of CO_2. Acidification, by increasing Pco_2, increased resting threshold, causing the fiber to become less excitable. Changes in extracellular pH alone cannot account for the changes in threshold in BC-CO_2 solution because no such changes in excitability were observed in the HEPES buffer over the same pH range. These results indicate either that the presence of HEPES buffer is preventing threshold changes with varying pH_e or that CO_2 itself was affecting resting threshold. To resolve these two possibilities, CO_2 was added to the HEPES buffered solution. The effects on resting threshold were similar to those observed in BC-CO_2 (Fig. 3); as the concentration of CO_2 increased, resting threshold also increased. Therefore, CO_2 has characteristic effects on resting threshold independent of the external pH or the presence of HEPES buffer.

Tonic Effects With Lidocaine Present

The concentration of lidocaine required to decrease the amplitude of the AP_c by 40% or to double the threshold is plotted as a function of pH in Figure 4. In HEPES solution adjusted with HCl and NaOH, more lidocaine was required at pH 6.4 to block the AP_c or to raise threshold than at pH 8.0. The opposite was observed in BC-CO_2 buffer with pH adjusted by CO_2; less lidocaine was needed at acid pH to block the AP_c (Fig. 4B) or to raise threshold (Fig. 4A). Lidocaine at pH 6.4 appears to be threefold to eightfold more potent in BC-CO_2 solution with CO_2 present

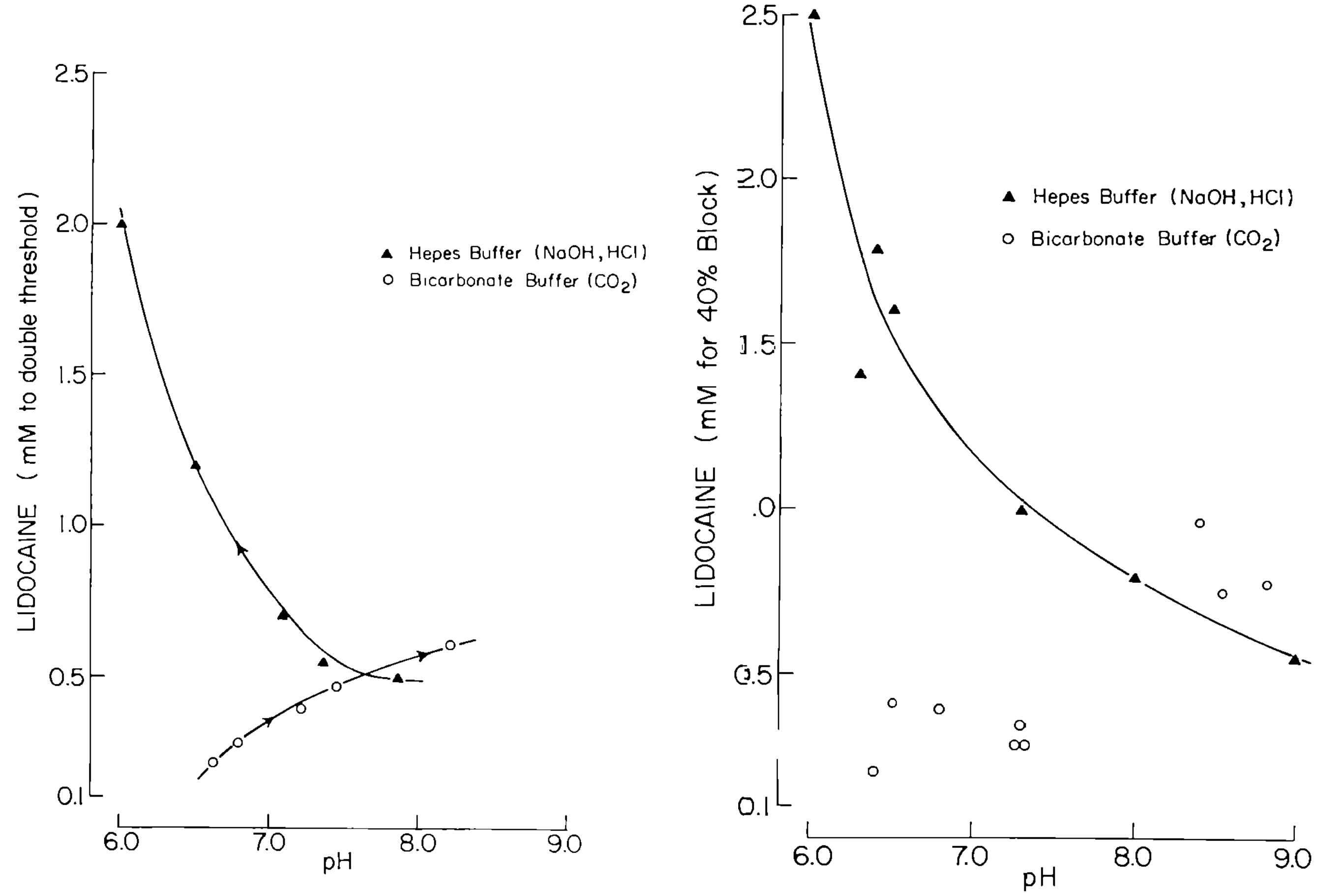

Figure 4. (A) Concentration of lidocaine required to double threshold. BC-CO_2 solution: a fiber conducting at 21 m/sec was equilibrated with BC-CO_2 solution at 10% P_{CO_2} (pH 6.65). Enough lidocaine was added to double the threshold (open circles). The proportion of CO_2 was diminished in stages to 0.2% at pH 8.2, and lidocaine was added as needed to "clamp" the threshold at the doubled value. All fibers studied (n = 6) showed a similar relation. HEPES solution: a fiber conducting at 20 m/sec was bathed in HEPES solution at pH 8. Enough lidocaine was added to double resting threshold (filled triangles). More lidocaine was added after each increment in HCl so as to hold the threshold at the elevated level. (B) Concentration of lidocaine required to produce a 40% decrease in the amplitude of the AP_c: For BC-CO_2 solution, open circles show the concentration of lidocaine yielding 40% block at each pH. For HEPES solution, triangles denote the concentration that would be required to give 40% block obtained from dose–response curves for block at each pH.

than in HEPES solution without CO_2. The potency of lidocaine was approximately the same in both conditions at pH 8.0 where neither solution contained much CO_2. We believe that the apparent increase in relative potency in BC-CO_2 occurred at least in part because the direct action of CO_2 added to the effect of the local anesthetic.

In both of the techniques used here, preliminary experiments identified the direction (acidification vs alkalization) in which *increasing* concentrations of lidocaine would be required to hold constant the elevated level of threshold or the amount of B_t. The experiments were then consistently performed by adjusting the pH in that direction, observing a drop in threshold or increase in AP_c and adding sufficient lidocaine to restore the original level of block. Because these titrations were slow, the total duration of exposure to the drug was several hours. As a check on the importance of prolonged exposure to degree of block, several pH values were selected, and a bolus of lidocaine added to the fresh nerve to confirm that a similar B_t of 40% was obtained within 30 min. Usually 15 min sufficed to reach steady state level. These experiments indicate that changing the solution pH so as to reduce block leads to a long-lasting requirement for increased concentration of anesthetic. The increase in concentration required to maintain a doubled threshold in single fibers exposed over 6 cm within the nerve sheath matched rather closely the increases in concentration required to hold block of the AP_c at 40% in desheathed nerves.

When lidocaine was used to reduce the margin of safety, we observed a blocking action of CO_2 on the compound action potential. Increasing P_{CO_2} reversi-

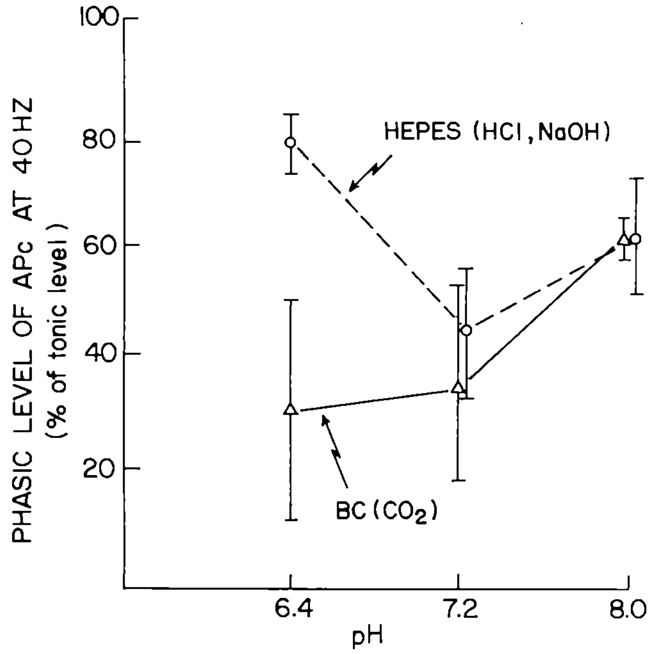

Figure 5. pH dependence of frequency-dependent block (B_f) in HEPES and BC-CO_2 solutions. The amplitude of the last AP_c of a 40 Hz burst is plotted as a percentage of the amplitude of the AP_c during tonic block stimulated once per minute vs pH. The mean standard deviation is shown. A two-tailed *t*-test showed that the difference in B_f was significant ($P < 0.02$) at pH 7.2 and 6.4.

bly decreased the amplitude of the AP_c in a nerve equilibrated with BC-CO_2 solution containing 0.5 mM lidocaine. This result is a second demonstration of the finding that less lidocaine is required to block impulses when CO_2 is present in BC-CO_2 solution (Fig. 4*B*), although it does not demonstrate that CO_2 is acting directly. Lidocaine already present in nerves may have been potentiated by CO_2. This is not a possibility for the threshold experiments, which do show a direct effect of CO_2.

Effects of pH on Activity-Dependence in BC-CO_2 and HEPES Solutions

During 10-sec trains of high-frequency stimulation in either control solution, the amplitude of the AP_c decreased by about 2%. In the presence of lidocaine, the same 40 Hz train caused a further transient decrease in the amplitude of the AP_c (B_f) from the level of B_t. Frequency-dependent block also varied with pH, being greater in BC-CO_2 solution at pH 6.4 than in HEPES solution at the same pH (Fig. 5). In BC-CO_2 solution at pH 8.0 (at low concentrations of CO_2), B_f was the same as in HEPES solution at pH 8.0. In HEPES solution, B_f was greatest at pH 7.2 and decreased in both acid and alkaline conditions. The presence of CO_2, then, appears to potentiate B_f as well as B_t from lidocaine.

Discussion

These studies permit a partial resolution of hypotheses concerning the combined actions of CO_2, lidocaine, and impulse activity on conduction block. The experiments involve at least three parallel actions: 1) Carbon dioxide acts as a membrane permeant acid that will increase the proportion of lidocaine in cationic form within the axon by acidifying the axoplasm (30,31). This action would "trap" the cationic form of lidocaine within the axon (11) and also might be expected to enhance its potency if the cationic form is a more effective channel blocker than the neutral form (16,32–35). Carbon dioxide may also enhance the availability of anesthetic to sites of action within the membrane, e.g., by increasing the concentration of the protonated form within the membrane through bicarbonate salt formation (17). 2) There may be a direct action of CO_2, either through acidifying the axoplasm, modulating axoplasmic free calcium (36), or through chemical combination with channel molecules or channel modulating molecules, e.g., as a carbamate. Because CO_2 was found to increase threshold in the absence of lidocaine, this direct effect also likely increases blocking action under conditions where anesthetic is present. And, 3) the acidification of the extraaxonal bathing solution will increase the proportion of lidocaine in polar form outside the fiber. Because acidification of the solutions in the absence of CO_2 reduced the steady state potency of lidocaine, this action would be expected to reduce the degree of block. Figure 6 summarizes the findings concerning the net result of these (and possibly other) opposing processes. When pH is shifted with impermeant buffers (the upper left box in Fig. 6), the potency of lidocaine, as gauged either by measurements of excitability or of AP_c, is greater in the alkaline range. Carbon dioxide acting without lidocaine present (upper right box in Fig. 6) raised threshold as the solution became acidic. Under conditions where CO_2 was added in the presence of lidocaine the two effects combined and, at least for the cases of marginal conduction block tested here, the net result at steady state was an increased tendency for conduction block.

Action of Carbon Dioxide

With no anesthetic present, we find that CO_2 increases the threshold of single fibers, but does not

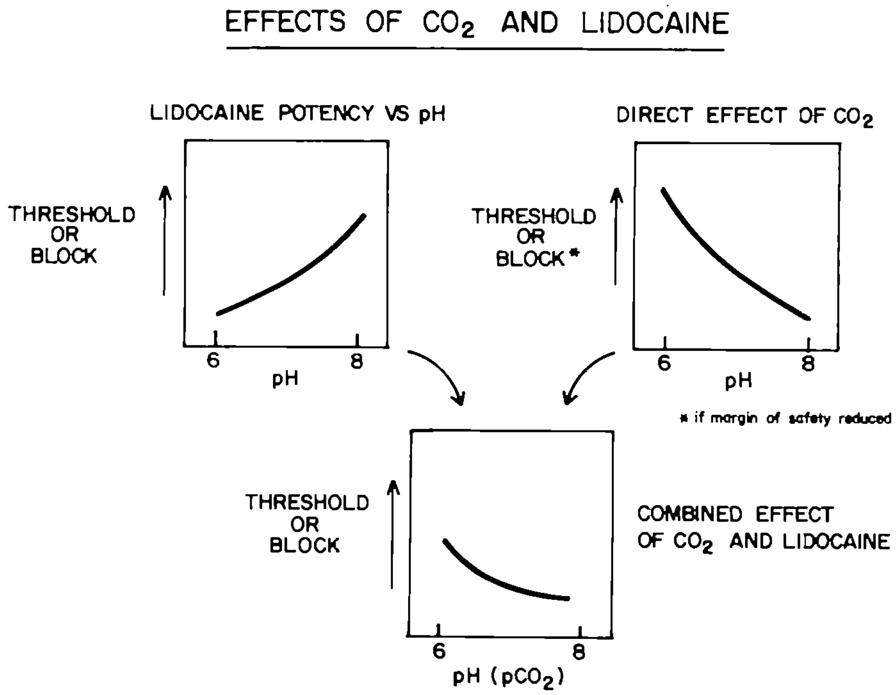

Figure 6. Summary of effects of CO_2 and lidocaine on nerve conduction. The upper left box indicates a direct relationship between pH and lidocaine potency as indicated by increased block of the AP_c or increased threshold in single fibers. Lidocaine appears more potent at pH 8.0. The upper right box indicates the direct effects of CO_2. As CO_2 increases, threshold increases in single fibers and block of the AP_c increases if the margin of safety for conduction has been compromised by adding lidocaine to the buffer solution. The lower box indicates the effects of CO_2 and lidocaine together. The apparent potency of lidocaine is greater at acid pH due in part to the direct effects of CO_2, which raises threshold and enhances block of impulses (see text).

reduce the AP_c. The increase in threshold is consistent with early work on the AP_c, which established that the current strength required of a stimulus pulse to hold the (submaximal) AP_c at a constant height was increased with increased P_{CO_2} for amphibian and mammalian nerve recorded in moist air chambers (1,4,3,18). A reversible increased threshold with CO_2 in single fibers was also found using isolated nodes of Ranvier from frog myelinated fibers (37) and unmyelinated crab axons (3). The degree of change in resting threshold of frog single A-fibers is substantial, with a steep dependence near pH 7.4. To produce an equivalent increase in threshold as seen here when sufficient CO_2 was added to BC-CO_2 at pH 8.0 to bring the pH to 7.0 (about 6% CO_2), approximately 0.4 mmol lidocaine would need to be added to a BC-CO_2 solution maintained at a constant pH of 7.4. The increase in threshold produced by CO_2 may reasonably be expected to deepen conduction block in conditions where conduction is already compromised.

A blocking action of CO_2 alone was observed by Catchlove (11), who recorded the AP_c on the far side of a 1 cm segment of frog sciatic nerve in Tris-buffered Ringers exposed to 50% CO_2 in O_2 for 5 min. The partial block (~30–50%) occurred in desheathed preparations, not in nerves with an intact sheath. We exposed approximately the same length of desheathed nerve to BC-CO_2 solution equilibrated with 0.2–10% CO_2 and noted no drop in AP_c height at steady state.

Changed pH

In desheathed frog nerves exposed to Ringer buffered with Tris and HCl to pH 5.5, Catchlove observed slight (~10%) blocking action in comparison to the same solution at pH 7.3. This may reflect the direct blocking action of H_3O^+ on sodium current (6,38,39), which would be significant at pH 5.5 and which might be sufficient to produce conduction block if the margin of conduction safety were reduced by desheathing. The observation that using NaOH or HCl to change pH_e has little effect on threshold of single myelinated fibers is consistent with results on whole nerves (1,4,3,15,18,40) and isolated nodes (3,41). The actions of CO_2 on accommodation, on excitability, and on conduction were not matched by equivalent pH changes under conditions where P_{CO_2} was unchanged. How CO_2 exerts its characteristic effects has not yet been established, although other authors have previously speculated on the role of internal pH (3,18,41).

With local anesthetic present, acidification by HCl under conditions of constant low P_{CO_2} in HEPES solutions lowered the potency of lidocaine. This finding supports earlier studies at atmospheric CO_2 in nerves with intact sheath, showing increased blocking as pH becomes more basic over the range of pH 6.5 to 8.0 (40,42,43). Our results do not indicate that strongly alkaline solutions of pH 9 are associated with reduced potency (15). However, both our AP_c and threshold measures show clearly that lidocaine potency in HEPES solutions depends more steeply on pH under acid conditions below pH 7.2.

The possibility has been raised that more rapid onset of block under alkaline conditions, where the more permeant, lipid-soluble, neutral form of local anesthetics predominates, could be misinterpreted as a greater steady state block (24,44). Because our exposure times were always at least 15 min and sometimes several hours, this possibility is not a probable factor in our experiments. Diffusional delays for action of lidocaine placed outside an isolated frog fiber node are less than 1 sec at pH 8.3 and block is complete within 5 sec at pH 6 (35). The distribution of lidocaine within desheathed frog sciatic nerve at neutral pH has been reported to be near steady state within 10 min for both AP_c height and concentration (45,10,16) and in about 20 min for AP_c of rabbit vagal nerves at room temperature (43,15). Based on measures of increased latency of single vagal A and C fibers, Fink and Cairns (46) concluded that steady state effects from lidocaine were reached in an average of 17 min with sheath intact and 13 min with sheath removed. For experiments in HEPES under acid conditions, more equilibration time was required than at neutral pH. However, because several hours were allowed for this equilibration, it seems likely that the present results reflect the steady state alterations in blocking actions of lidocaine produced by pH changes rather than altered dynamics. Once a stable raised threshold was attained at a particular pH for a given concentration of lidocaine, subsequent cycling between higher or lower P_{CO_2} produced only transient shifts in threshold. Threshold returned to the original level upon restoration of the original conditions. Similar findings have been made for CAP height while CO_2 was varied with fixed concentration of either lidocaine (11) or bupivacaine (23,24). These results show that the same level of block will obtain at equilibrium regardless of the P_{CO_2} profile during onset, which implies that P_{CO_2} may be used to affect the rate of block without perturbing the ultimate degree of block expected for a particular constant P_{CO_2}. Furthermore, transiently increasing the degree of local anesthetic action by increasing CO_2 appears to be rapidly and completely reversible.

Carbon Dioxide and Anesthetic Potency

For a variety of both amphiphilic and neutral anesthetics, CO_2 increases the degree of block whether the pH is held constant (18,11,23,24,44) or allowed to vary (1983). These experiments indicate that the apparent potency of lidocaine for conduction block in solutions with organic buffers such as HEPES differs from its apparent potency in solutions buffered with bicarbonate. Laboratory investigations on the mechanism of action of local anesthetics have used membrane-impermeant buffers such as HEPES, Tris, MES, or MOPS (16,32,42,47) to determine whether it is the cation or the uncharged amine that is the active form of the local anesthetic molecule, one that combines with a receptor in the nerve membrane to produce conduction block. Such experiments do not account for the independent action of CO_2 and may not correlate with physiologic conditions in vivo where CO_2 tension is an important factor in regulation of the pH of body fluids and cytoplasm. In our experiments, we demonstrate that lidocaine appears to be several times more potent at pH 6.4 in BC-CO_2 solutions than at the same pH in HEPES solutions, as determined by measurement of threshold, B_t and B_f. In previous work, CO_2 increased by about tenfold the blocking action of procaine at pH 7.4 for nerves with sheath intact (18).

The mechanism of the action of CO_2 on axon membranes is not clear. Whether CO_2 acts in the molecular form or through lowering pH_i (30) cannot be decided from these experiments because pH_i was not measured. We can conclude, however, that the action of CO_2 in potentiating block is not caused directly by changes in pH_e because the pH changes with HCl and NaOH in HEPES buffer had such different effects on threshold, B_t, and B_f from those with CO_2 in BC-CO_2 buffer. These in vitro experiments suggest that respiratory acidosis encountered in the clinical situation produces a depressant effect that adds to lidocaine conduction block and that may contribute to the toxic reactions observed. It is known that toxic effects are provoked to a greater extent by respiratory acidosis than by metabolic acidosis (48).

We thank Richard F. Roscoe Jr for excellent technical assistance and Rachel Abrams for secretarial work.

References

1. Lehmann JE. The effect of changes in pH on the action of mammalian A fibers. Am J Physiol 1937;118:600–12.
2. Hettwer JP. The relation of threshold of excitability of nerve to carbon dioxide tension. Am J Physiol 1938;122:275–80.
3. Coraboeuf E. Analyse electrophysiologique de l'action de l'anhydride carbonique sur le nerf isolé. J Physiol (Paris) 1954;46:745–75.
4. Lorente de No R. Carbon dioxide and nerve function. In: A study of nerve physiology. Studies from the Rockefeller Institute for Medical Research 1947;131:148–94.
5. Hille B. Charges and potentials at the nerve surface: divalent ions and pH. J Gen Physiol 1968;51:221–36.

6. Woodhull AM. Ionic blockage of sodium channels in nerve. J Gen Physiol 1973;61:687–708.
7. Hille B, Woodhull AM, Shapiro BI. Negative surface charge near sodium channels of nerve: divalent ions, monovalent ions, and pH. Philos Trans R Soc Lond 1975;70:301–18.
8. Toman JEP. Neuropharmacology of peripheral nerve. Pharmacol Rev 1952;4:168–218.
9. Bianchi CP, Strobel GE. Modes of action of local anesthetics in nerve and muscle in relation to their uptake and distribution. Trans NY Acad Sci 1968;30:1082–92.
10. Strobel GE, Bianchi CP. The effects of pH gradients on the uptake and distribution of C^{14}-procaine and lidocaine in intact and desheathed sciatic nerve trunks. J Pharmacol Exp Ther 1970;172:18–32.
11. Catchlove RFH. The influence of CO_2 and pH on local anesthetic action. J Pharmacol Exp Ther 1972;181:298–309.
12. Hille B. The pH-dependent rate of action of local anesthetics on the node of Ranvier. J Gen Physiol 1977;69:475–96.
13. Skou JC. Local anesthetics. I. The blocking action of some local anesthetics and of butyl alcohol on peripheral nerves. Acta Pharmacol Toxicol 1954;10:281–91.
14. Ritchie JM, Greengard P. On the mode of action of local blocking anesthetics. Annu Rev Pharmacol Toxicol 1966;6:405–30.
15. Ritchie JM, Ritchie BR. Local anesthetics: effect of pH on activity. Science 1968;162:1394–5.
16. Strobel GE, Bianchi PE. The effects of pH gradients on the action of procaine and lidocaine in intact and desheathed sciatic nerves. J Pharmacol Exp Ther 1970;172:1–17.
17. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesthesiol Scand 1965;16(suppl):55–69.
18. Condouris GA, Shakalis A. Potentiation of the nerve depressant effects of local anaesthetics by carbon dioxide. Nature 1964;204:57–9.
19. Bromage PR, Burfort MF, Crowell DE, Truant AP. Quality of epidural blockade III. Carbonated anaesthetic solutions. Br J Anaesth 1967;39:197.
20. Schulte-Steinberg D, Hartmuth J, Schutt L. Carbon dioxide salts of lignocaine in brachial plexus block. Anaesthesia 1970;25:191–7.
21. Morison DH. A double-blind comparison of carbonated lidocaine and lidocaine hydrochloride in epidural anesthesia. Can Anaesth Soc J 1981;28:387–9.
22. Raymond SA, Bokesch PM. Effects of CO_2/bicarbonate vs. an organic buffer on nerve threshold and local anesthetic block at varying pH. Anesthesiology 1983;59:A295.
23. Catchlove RFH. Potentiation of two different local anaesthetics by carbon dioxide. Br J Anaesth 1973;45:471–4.
24. Gissen AJ, Covino BG, Gregus J. Differential sensitivity of fast and slow fibres in mammalian nerve. IV. Effect of carbonation of local anesthetics (LA). Reg Anesth. 1985;10:68–75.
25. Stämpfli R. A new method for measuring membrane potentials with external electrodes. Experientia 1954;10:508–9.
26. Condouris GA, Goebel RH, Brady T. Computer simulation of local anesthetic effects using a mathematical model of myelinated nerve. J Pharmacol Exp Therap 1976;196:737–45.
27. Raymond SA, Roscoe R. Effects of lidocaine on threshold of nerve axons. Reg Anesth 1984;9:51.
28. Raymond SA. Effects of nerve impulses on threshold of frog sciatic nerve fibre. J Physiol 1979;290:273–303.
29. Tasaki I. Nervous transmission. Springfield, Illinois: CC Thomas 1953:164.
30. Boron WF, DeWeer P. Intracellular pH transients in squid giant axons caused by CO_2, NH_3, and metabolic inhibitors. J Gen Physiol 1967;67:91–112.
31. Abercrombie RF, Putman RW, Ross A. The intracellular pH of frog skeletal muscle: its regulation in isotonic solutions. J Physiol 1983;345:175–87.
32. Narahashi T, Frazier DT, Yamada M. The site of action and active form of local anesthetics. I. Theory and pH experiments with tertiary compounds. J Pharmacol Exp Ther 1970;171:32–44.
33. Frazier DT, Narahashi T, Yamada M. The site of action and active form of local anesthetics. II. Experiments with quaternary compounds. J Pharmacol Exp Ther 1970;171:45–51.
34. Strichartz GR. The inhibition of sodium currents in myelinated nerve by quaternary derivatives of lidocaine. J Gen Physiol 1973;62:37–57.
35. Hille B. Local anesthetics: hydrophilic and hydrophobic pathways for the drug–receptor reaction. J Gen Physiol 1977;69:497–515.
36. Schaer H. Decrease in ionized calcium by bicarbonate in physiological solutions. Pflügers Archiv 1974;347:249–54.
37. Niedergerke R, Stämpfli, R. Die Kohlensäurewirkung an der einzelnen markhaltigen Nervenfaser bei Rheobasenbestimmungen. Pflügers Archiv 1953;258:95–102.
38. Drouin H, Thé R. The effect of reducing extracellular pH on the membrane currents of the Ranvier node. Pflügers Arch. 1969;313:80–8.
39. Mozhayeva GN, Naumov AP, Nosyreva ED. A study on the potential-dependence of proton block of sodium channels. Biochim Biophys Acta 1984;775:435–40.
40. Rud J. Local anesthetics. An electrophysiological investigation of local anesthesia for peripheral nerves with special reference to xylocaine. Acta Physiol Scand 1961;51(suppl 178):1–171.
41. Coraboeuf E, Niedergerke R. Kohlensäure- und pH-Wirkung an der markhaltigen Einselfaser des Froschs. Pflügers Archiv 1953;258:103–7.
42. Ritchie JM, Ritchie B, Greengard P. The active structure of local anesthetics. J Pharmacol Exp Ther 1965;150:152–9.
43. Ritchie JM, Ritchie B, Greengard P. The effect of the nerve sheath on the action of local anesthetics. J Pharmacol Exp Ther 1965;150:160–4.
44. Wildsmith JAW, Gissen AJ, Gregus J, Covino BG. Differential nerve blocking activity of amino-ester local anaesthetics. Br J Anaesth 1985;57:612–20.
45. Bennett AL, Wagner JC, McIntyre AR. The determination of local anesthetic potency by observation of the nerve action potential. J Pharmacol Exp Therap 1942;75:125–36.
46. Fink BR, Cairns AM. Diffusional delay in local anesthetic block in vitro. Anesthesiology 1984;61:555–7.
47. Schwarz W, Palade PT, Hille B. Local anesthetics. Effect of pH on use-dependent block of sodium channels in frog muscle. Biophys J 1977;20:343–68.
48. Englesson S, Grevsten S. The influence of acid–base changes on central nervous system toxicity of local anaesthetic agents. I. Acta Anaesth Scand 1974;18:88–103.

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Paresthesias and Motor Dysfunction after Labor and Delivery

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ONG BY, COHEN MM, ESMAIL A, CUMMING M, KOZODY R, PALAHNIUK RJ. Paresthesias and motor dysfunction after labor and delivery. Anesth Analg 1987;66:18–22.

The incidence of paresthesias and motor dysfunction associated with 23,827 deliveries at Winnipeg Women's Hospital during a 9-yr period (1975–1983) was 18.9/10,000 deliveries. All the symptoms resolved within 72 hr after supportive therapy only. The frequency of paresthesias and motor dysfunction was greater in primiparas, women who had forceps- or vacuum-assisted deliveries, and women who had epidural or general anesthesia. Significant neurologic deficits after labor and delivery with or without epidural anesthesia were rare. Epidural anesthesia is a safe technique in this regard.

Key Words: ANESTHESIA—obstetric. ANESTHETIC TECHNIQUES—epidural. PREGNANCY—complications.

A major concern for the obstetric patient and her anesthesiologist in choosing regional anesthesia for analgesia during labor is the risk of neurologic deficit after delivery. Obstetric patients may develop paresthesias and motor dysfunction in the postpartum period in association with a number of factors, including prolonged blockade by a local anesthetic (1,2), nerve entrapment (3,4), prolapsed intervertebral disc (5), trauma of delivery (6–9), malpositioning during delivery (10,11), epidural anesthesia (12–17), adhesive arachnoiditis (18,19), etc. Most of the literature related to these problems consists of case reports and series devoted to one possible etiologic factor. The estimated incidence of motor or sensory dysfunction in a lower extremity after labor and delivery ranged from 1:2600 in the older obstetric literature (8) to nil in more recent reports (20–22). However, there are no data that would be applicable to a general obstetric population. Therefore, we reviewed the records of obstetric patients who delivered at the Winnipeg Women's Hospital during a 9-yr period (1975–1983) to determine the incidence and nature of postpartum paresthesias and motor dysfunction.

Method

An Obstetric Anesthesia Followup Program was in operation at the Women's Hospital in Winnipeg during the period from 1975 to 1983. This hospital is one of two major referral hospitals for a population of about 1.5 million people and also functions as a community hospital for women in the adjacent neighborhoods. The Department of Anesthesia provides 24-hr coverage with an anesthesiologist on duty in the hospital at all times. A specially trained anesthesia nurse reviewed each obstetric patient's chart and interviewed all patients who received an anesthetic to identify complications possibly associated with anesthesia. The definition of the complications sought did not vary over the study period. The chart review included the antepartum record, labor and delivery records, and the anesthesia record. Specific conditions complicating the pregnancy or delivery were also identified. To validate the database, it was computer-linked to records from Manitoba's universal health insurance plan. There was excellent agreement between the two data files.

From the database, all obstetric patients with paresthesias, neurologic deficits, or motor deficits in the postpartum period were identified. The hospital charts for these patients were then manually reviewed to determine the specific symptoms. Because the database is based on the number of infants rather than the number of women who gave birth, the results are expressed as the percentage of babies delivered or as complications per 10,000 deliveries. The data were analyzed by χ^2 analysis to determine statistical significance.

Supported by a National Health Research Development Program Postdoctoral Fellowship to M. M. Cohen.

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Table 1. Analgesia and Anesthesia Provided for Vaginal Delivery and Cesarean Section

Type of analgesia and anesthesia	Number of deliveries	Percent of total deliveries
None	8198	34.4
Inhalational analgesia	4766	20.0
Epidural anesthesia	9403	39.5
General anesthesia	864	3.6
Other	381	1.6
Not coded	215	0.9%

Table 2. Incidence of Paresthesia and Motor Dysfunction among Patients with Different Characteristics

Patient characteristics	Incidence of symptoms (per 10,000 deliveries)	*P*
Multiparas	11.7	—
Primiparas	27.9	<0.02[a]
Spontaneous vaginal deliveries	11.0	—
Forceps/vacuum assisted deliveries	28.5	<0.03[b]

[a] Compared to multiparas.
[b] Compared to spontaneous vaginal deliveries.

Results

From 1975 to 1983, 33,698 deliveries occurred at the Winnipeg Women's Hospital. Of these, 23,827 (70.7%) charts were reviewed and 15,414 (45.7%) patients were interviewed by the follow-up nurse. Those not included were patients who delivered while the nurse was on holiday or whose data were removed because of coding or transcription errors.

Of the 23,827 deliveries in our review, 12,725 (53.4%) were spontaneous vaginal deliveries, 6651 (27.9%) were forceps- or vacuum-assisted deliveries, and 4451 (18.6%) were cesarean sections. The analgesia or anesthesia provided for these deliveries is listed in Table 1.

From the 23,827 records, 45 cases of neurologic deficits were identified, an incidence of 18.9/10,000 deliveries. The incidence was significantly greater in primiparas than in multiparas ($P < 0.02$), and was significantly greater in parturients who had forceps- or vacuum-assisted deliveries than in those who had spontaneous vaginal deliveries ($P < 0.03$) (Table 2). Parturients who had epidural or general anesthesia also had a higher incidence of neurologic deficits than parturients who had no anesthesia or who had only inhalational analgesia ($P < 0.001$) (Table 3). There was no difference in incidence between parturients who had diabetes mellitus and those who did not.

Table 3. Incidence of Paresthesia and Motor Dysfunction after Different Analgesia and Anesthesia Techniques

Analgesia and anesthesia technique	Incidence of symptoms (per 10,000 deliveries)	*P*
None	2.4	—
Inhalational analgesia only	6.3	ns[a]
Epidural anesthesia	36.2	<0.001[a]
General anesthesia	34.7	<0.001[a]

Abbreviation: ns, not significant.
[a] Compared to no analgesia or anesthesia.

Table 4. Previously Reported Etiologies of Postpartum Paresthesia and Motor Dysfunction

Etiology reported	References
Adhesive arachnoiditis	18,19
Epidural anesthesia	12,14
Epidural vascular malformation	25,26,27
Epidural hematoma	31
Iliopsoas muscle strain	29
Malpositioning during delivery	10,11
Nerve entrapments	3,4
Preservative in epidural solution	32
Prolapsed intervertebral disc	5
Prolonged blockade by local anesthetic	1,2
Relapsing idiopathic polyneuritis	28
Spinal cord tumor	24
Trauma of delivery	6,7,8,9
Unrelated to anesthesia or delivery	30

The intensive review of the obstetric and anesthesia records of these 45 patients showed that paresthesias or motor deficits were documented in only ten of the patients' charts. As the anesthesia follow-up nurse was not a member of the regular hospital staff, she did not record her findings on the patients' charts.

All the deficits documented in the charts were temporary, with full recovery in less than 72 hr in all cases. A review of all the charts did not show any evidence of residual neurologic deficit at discharge in any patient.

Discussion

Paresthesias and motor dysfunction in the postpartum period have been associated with a variety of factors (Table 4). The listing is not intended to be exhaustive but to indicate the large number of possible etiologies that must be considered in the differential diagnosis of postpartum neurologic symptoms.

The 34 deficits among the 9403 deliveries per-

Table 5. Incidence of Paresthesia after Epidural Anesthesia in Previous Reports

Source	Number of cases	Incidence per 10,000
Crawford (13)	2035	14.7
Eisen et al. (17)	9532	16.8
Abouleish (14)	1417	42.3
Lund (16)	10,000	5.0
Bonica et al. (15)	3637	24.7

Table 6. Incidence of Motor Deficit after Epidural Administration in Previous Reports

Source	Number of cases	Incidence per 10,000
Dawkins (12)	32,718	transient, 14.7; permanent, 2.1
Crawford (13)	2035	0
Abouleish (14)	1417	14.1
Bonica et al. (15)	3637	2.7
Lund (16)	10,000	1
Hellman (20)	26,127	0
Moore et al. (21)	6729	0
Bleyaert (22)	3000	0

formed with epidural anesthesia, for an incidence of 36.2/10,000 deliveries, is slightly higher than some previous reports (Table 5). However, only nine of the 34 cases were documented in the chart. If we used the figure of nine to calculate the incidence, the rate would be 9.6/10,000, which is quite similar to the incidence rates reported in retrospective series (13,15–17). Abouleish (14) reported a slightly higher incidence of 6/1417 or 42.3/10,000, which is similar to our follow-up data. Two of the patients in Abouleish's series complained only of tingling sensations in a lower limb without any objective neurologic findings; these would not likely be identified except in a prospective study specifically looking for such symptoms.

Most of the deficits that were identified were transient numbness or tingling sensory disturbances. Many of these changes occurred in the lateral aspects of the thighs or the dorsal surfaces of the feet and might be explained by compression of the lateral femoral cutaneous nerve or the peroneal nerve. Such peripheral nerve complications are mainly the result of inappropriate positioning in the lithotomy position. The anesthetics provided may have contributed by suppressing the discomforts produced by nerve compression or by decreasing the normal muscle tone and allowing excessive stretching of the nerves.

One of the patients in our series developed a foot drop after a difficult Kjelland's forceps rotation under epidural anesthesia. Another patient, who had pudendal nerve infiltration during the second stage of labor, had bladder dysfunction in the postpartum period.

The incidence of motor dysfunction is 0.8/10,000 in our series. The incidences of motor deficits in previous reports of epidural administrations are listed in Table 6. Although Abouleish (14) and Dawkins (12) have reported higher incidences, the other six reports showed incidences as low as ours. In contrast, the incidence of lower limb paralysis has been reported to be 1:2600 (6,8) to 1:6400 (7) in the older obstetric literature. The obstetric reports usually involve prolonged labor and forceps delivery. The difference between older reports and more recent data may therefore be explained by the changes in obstetric management of difficult deliveries.

That the incidence of symptoms among parturients who had epidural anesthesia was similar to that in patients who had general anesthesia is interesting. There is no previous estimate of the prevalence of neurologic deficit after labor and delivery associated with general anesthesia. Schreiner et al. (23) suggested that the prevalence of paralysis associated with, but unrelated to anesthesia, was about 1:6000 in surgical patients based on cases that came to their attention in a referral hospital. A more diligent search would probably have identified other patients with less severe symptoms.

The greater incidence of symptoms among primiparas and those who had instrument-assisted deliveries is consistent with previous reports. In the obstetric series, postpartum motor dysfunction usually occurs in nulliparas after forceps-assisted deliveries. In Abouleish's series (14), five of the six (83.3%) patients who developed neurologic symptoms in the postpartum period had forceps-assisted deliveries and two of the five had muscle paresis.

Parturients who received epidural or general anesthesia are more likely to be patients who have longer and more difficult labors, have forceps- or vacuum-assisted deliveries, or otherwise are at higher risk to develop paresthesias. A direct relationship between postpartum neurologic deficits and epidural anesthesia would be difficult to prove and is, in fact, highly unlikely in our opinion.

Two of the patients in our series who developed postpartum symptoms had a history of back pain significant enough to be noted in the chart. In one of these cases, the attending anesthesiologist diagnosed the cause of the postpartum neurologic deficit as prolonged blockade by local anesthetic solution (0.375%

bupivacaine). No exacerbation of back pain was noted in either case. Diabetic women did not have a higher incidence of neurologic complications than nondiabetic women. Either preexisting diseases have no significant effect on development of postpartum neurologic complication or the selective exclusion of patients at high risk may explain the paucity of patients with preexisting diseases who developed postpartum neurologic complications.

Most of the patients in our series received lidocaine hydrochloride, lidocaine carbonate, or bupivacaine for epidural analgesia. Because many patients received two of these agents, no association with any particular local anesthetic could be determined. 2-Chloroprocaine was used infrequently and there were insufficient cases to comment on its possible relation to postpartum neurologic deficits.

A discouraging finding of this study is that many of the neurologic deficits identified by the follow-up nurse were not properly documented in the patients' charts. The possible explanations for this finding include the short duration and minor nature of most of the neurologic deficits, early discharge of the patients, and failure of the attending staff to recognize minor nerve injuries. Nine of the ten cases that were documented in the chart had an epidural anesthetic and these patients may have been observed more closely for paresthesia or motor dysfunction in the postpartum period by the medical and nursing staffs.

The follow-up system with a trained nurse can identify most of the major neurologic deficits in the postpartum period. Although the nurse did not interview all patients who delivered, she reviewed the charts of the other patients and she was in close communication with the ward nurses who looked after the patients directly. Some cases of deficit would have been missed if they developed after discharge from hospital. For example, one patient who had an inadvertent dural puncture during insertion of an epidural catheter developed transient sixth cranial nerve palsy after discharge. On the other hand, a patient with minor psychogenic symptoms could be included in the database and would result in a false positive occurrence. To minimize these errors, close cooperation and appropriate input from the attending physicians is required.

In summary, the incidence of paresthesias and motor dysfunctions after delivery of an infant was 18.9/10,000. All the symptoms were of brief duration, with full recovery after supportive therapy only. These results support the clinical impression that significant neurologic deficits after labor and delivery with or without regional anesthesia are rare, and that epidural anesthesia is a safe technique in this regard.

References

1. Downing JW. Bupivacaine: a clinical assessment in lumbar extradural block. Br J Anaesth 1969;41:427–32.
2. Pathy GV, Rosen M. Prolonged block with recovery after extradural analgesia for labour. Br J Anaesth 1975;47:520–2.
3. Rhodes P. Meralgia paraesthetica in pregnancy. Lancet 1957;ii:831.
4. Pearson MG. Meralgia paraesthetica with reference to its occurrence in pregnancy. Br J Obstet Gynaecol 1957;64:427–30.
5. O'Connell JEA. Lumbar disc protrusions in pregnancy. J Neurol Neurosurg Psychiatry. 1960;23:138–41.
6. Tillman AJB. Traumatic neuritis in the puerperium. Am J Obstet Gynecol 1935;29:660–6.
7. Cole JT. Maternal obstetric paralysis. Am J Obstet Gynecol 1946;52:372–86.
8. Hill EC. Maternal obstetric paralysis. Am J Obstet Gynecol 1964;88:399–403.
9. Murray RR. Maternal obstetrical paralysis. Am J Obstet Gynecol 1964;88:399–403.
10. Slocum HC, O'Neal KC, Allen CR. Neurovascular complications from malposition on the operating table. Surg Gynecol Obstet 1948;86:729–34.
11. Burkhart FL, Daly JW. Sciatic and peroneal nerve injury: a complication of vaginal operations. Obstet Gynecol 1966; 28:99–102.
12. Dawkins CJM. An analysis of the complications of extradural and caudal block. Anaesthesia 1969;24:554–63.
13. Crawford JS. The second thousand epidural blocks in an obstetric hospital practice. Br J Anaesth 1972;44:1277–87.
14. Abouleish E. Neurologic complications following epidural analgesia in obstetrics. Reg Anesth 1982;7:119–24.
15. Bonica JJ, Backup PH, Anderson CE, Hadfield D, Crepps WF, Monk BF. Peridural block: analysis of 3367 cases and a review. Anesthesiology 1957;18:723–84.
16. Lund PC. Peridural Anaesthesia. A review of 10,000 administrations. Acta Anaesthesiol Scand 1962;6:143–59.
17. Eisen SM, Rosen N, Winesanker H, et al. The routine use of epidural anaesthesia in obstetrics: a clinical review of 9532 cases. Can Anaesth Soc J 1960;7:280–9.
18. Reisner LS, Hochman BN, Plumer MH. Persistent neurologic deficit and adhesive arachnoiditis following intrathecal 2-chloroprocaine injection. Anesth Analg 1980;59:452–4.
19. Ravindran RS, Bond JK, Tasch MD, Gupta CD, Luerssen TG. Prolonged neural blockade following regional analgesia with 2-chloroprocaine. Anesth Analg 1980;59:447–51.
20. Hellmann K. Epidural in obstetrics: a second look at 26,127 cases. Can Anaesth Soc J 1965;12:398–404.
21. Moore DC, Bridenbaugh LD, Thompson GE, Balfour RI, Horton WG. Bupivacaine: a review of 11,080 cases. Anesth Analg 1978;57:42–53.
22. Bleyaert A, Soetens M, Vaes L, Van Steenberge AL, VanderDonck A. Bupivacaine, 0.125 per cent, in obstetric epidural analgesia. Anesthesiology 1979;51:435–8.
23. Schreiner EJ, Lipson SF, Bromage PR, Camporesi EM. Neurological complications following general anaesthesia. Anaesthesia 1983;38:226–9.
24. Mealey J, Carter JE. Spinal cord tumor during pregnancy. Obstet Gynecol 1968;32:204–9.
25. Fields WS, Jones JR. Spinal epidural in hemangioma in pregnancy. Neurology 1957;7:825–8.
26. Nelson DA. Spinal cord compression due to vertebral angiomas during pregnancy. Arch Neurol 1964;11:408–13.

27. Hirsch NP, Child CS, Wigetilleka SA. Paraplegia caused by spinal angioma—possible association with epidural analgesia. Anesth Analg 1985;64:937–40.

28. Novak DJ, Johnson KP. Relapsing idiopathic polyneuritis during pregnancy. Immunological aspects and literature review. Arch Neurol 1973;28:219–23.

29. Shin YK, Lee VC, Kim YD. Unusual cause of weakness of the lower extremity following vaginal delivery under epidural analgesia: iliopsoas muscle strain. Anesthesiology 1985;63:531–3.

30. Ravindran RS, Viegas OJ. Transient lower extremity weakness in an obstetric patient unrelated to epidural anesthesia. Anesth Analg 1981;60:527–8.

31. Ballin NC. Paraplegia following epidural analgesia. Anaesthesia 1981;36:952–3.

32. Craig DB, Habib GG. Flaccid paraparesis following obstetrical epidural anesthesia: possible role of benzyl alcohol. Anesth Analg 1977;55:219–21.

Negative Inotropic Effects of Halothane, Enflurane, and Isoflurane in Papillary Muscles from Diabetic Rats

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Negative inotropic effects of halothane, enflurane, and isoflurane in papillary muscles from diabetic rats.
1987;66:23–8.

Myocardial contractile responses to halothane, enflurane, and isoflurane were studied in papillary muscles isolated from streptozotocin-induced diabetic rats and in those from age-matched control rats. The developed tension in diabetic papillary muscles electrically paced at a constant rate was not different from that in control muscles, but both the time to peak tension and the relaxation time of the isometric contraction were significantly prolonged in diabetic muscles. Halothane, enflurane, and isoflurane all produced negative inotropic effects in both diabetic and control muscles. However, the negative inotropic effects were significantly less in the muscles from diabetic rats than in the muscles from control rats throughout the range of concentrations. In muscles from both the diabetic and control rats, the negative inotropic effects of these anesthetics were accompanied by decreases in the time to peak tension and in relaxation time. The results suggest that the myocardium from the diabetic rat is less sensitive to the negative inotropic action of volatile anesthetics than is the myocardium of normal hearts.

Key Words: ANESTHETICS, VOLATILE—halothane, enflurane, isoflurane. HEART—contractility. COMPLICATIONS—diabetes mellitus. METABOLISM—diabetes mellitus.

Cardiovascular disease is a major cause of mortality in human diabetes mellitus (1). Although atherosclerosis of the coronary arteries may be responsible for a percentage of this mortality, there is also evidence of a specific diabetic cardiomyopathy independent of coronary artery disease and hypertension (2–4).

Cardiac dysfunction in diabetes has been evaluated in experimental animals in which diabetes was induced by chemical agents such as alloxan or streptozotocin that selectively destroy the β cells of the pancreas (5). Regan et al. (6) have shown abnormalities of left ventricular diastolic compliance in the diabetic dog. In addition, in vitro studies using isolated perfused hearts (7) and papillary muscles (8,9) obtained from rats with chemically induced diabetes have demonstrated that abnormalities in cardiac contractile function are associated with a marked retardation in relaxation.

Halothane is known to depress cardiac contractility not only in clinical situations and in animal in situ hearts (10–12), but also in isolated heart muscle preparations (13–15). A similar negative inotropic effect is also induced by enflurane (16) and isoflurane (17). Previous studies have reported that pathologic states such as myocardial ischemia (18,19) and congestive heart failure (16,17,20) alter the negative inotropic responses to volatile anesthetics. Thus it would be of interest to examine the negative inotropic effects of volatile anesthetics on diabetic cardiac muscles in which contractile functions might be impaired.

The present study was undertaken to evaluate the inotropic responses to halothane, enflurane, and isoflurane in papillary muscles isolated from streptozotocin-induced diabetic rats, and to compare these responses with those from age-matched control rats.

Methods

Male Wistar rats, 160–210 g, were made diabetic at 8 weeks with a single tail-vein injection of streptozotocin (50 mg/kg). The streptozotocin was dissolved in a citrate buffer solution (0.1 M citric acid and 0.2 M sodium phosphate, pH 4.5). Control rats were injected with the citrate buffer solution alone. All rats were provided with food and water ad libitum until they were killed. Eight weeks after the streptozotocin injection, the diabetic state was assessed by mea-

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Received from the Departments of Pharmacology and Anesthesiology, Hokkaido University School of Medicine, Sapporo, Japan. Accepted for publication July 31, 1986.

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Table 1. Body Weight, Heart Weight, and Plasma Glucose Levels in Control and Diabetic Rats

	Control	Diabetic	P
Body weight (g)	282 ± 6 (30)	154 ± 5 (30)	<0.001
Heart weight (mg)	720 ± 14 (27)	477 ± 15 (27)	<0.001
Plasma glucose (mg/dl)	169 ± 6 (23)	740 ± 24 (23)	<0.001

Results are expressed as mean ± SEM. Number of animals is given in parentheses. Statistical significance was determined by Student's *t*-test for unpaired data.

Table 2. Mechanical Parameters of Isometric Contractions in Control and Diabetic Rat Papillary Muscles Electrically Paced at 0.5 Hz

	Control	Diabetic	P
Peak developed tension (mg)	324 ± 29	314 ± 23	>0.5
Time to peak tension (msec)	104 ± 2	124 ± 2	<0.001
Time to ½ relaxation (msec)	67 ± 1	91 ± 2	<0.001

Results are expressed as mean ± SEM of 30 preparations. Statistical significance was determined by Student's *t*-test for unpaired data.

surement of plasma glucose (obtained during ether anesthesia) using the glucose oxidase method. Only animals with plasma glucose concentrations exceeding 500 mg/dl were considered to be diabetic and used for the experiments.

Animals were killed by a blow on the head 8 weeks after the injection of streptozotocin. The hearts were quickly removed and placed in a dissection bath filled with Krebs–Henseleit solution at room temperature. The papillary muscle was carefully dissected from the left ventricle and then mounted vertically in a water-jacketed bath containing 10 ml of Krebs-Henseleit solution with the following composition (mM): NaCl 119, $CaCl_2$ 2.5, KCl 4.8, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 24.9, and glucose 10.0. The solution in the bath was aerated with 95% O_2 and 5% CO_2 and kept at a constant temperature of 30 ± 1°C. The muscle was stimulated by square pulses of 0.5 Hz in frequency, 5 msec in duration, and double threshold voltage. The pulses were delivered by a pair of spiral platinum electrodes connected to an electronic stimulator (Sanei-Sokki 3F46) through an isolation unit (Sanei-Sokki 5361). Isometric tension, under a resting tension of 0.5–1 g, was recorded with a force transducer (Nihon Kohden TB-612T) and displayed on a pen recorder (Nihon Kohden RJG-3026) through a preamplifier (Nihon Kohden RP-5).

After a 60–90 min period of equilibration at a stimulation rate of 0.5 Hz, the isometric contractile parameters of the preparations, including the peak developed tension, time to peak tension, and time to half relaxation, were recorded. Then the effects of halothane, (Takeda, Osaka, Japan), enflurane (Abbot, Chicago, Illinois), and isoflurane (Ohio, Madison, Wisconsin) were studied. The anesthetics were introduced into the oxygen–carbon dioxide mixture through appropriate vaporizers. The Fluotec Mark 3 (Cyprane Keighley), Enflurane Vaporizer E3 (Kimura), and Isoflurane Vaporizer 19.1 (Drägerwerk) were used for halothane, enflurane, and isoflurane, respectively. The concentrations of the anesthetics in the bath medium were determined by gas chromatography (Shimadsu Gas Chromatograph GC-4A PTF). Concentration–response curves for the inotropic effects of the anesthetics were obtained in a cumulative manner by the stepwise addition of the anesthetics in the gas mixture. When the response to a given concentration reached a maximum, determinations of the above parameters of the isometric contractions were repeated and the next concentration was then administered.

All data are presented as mean values ± SEM. The statistical significance of the differences between control and diabetic groups was evaluated with Student's *t*-test for unpaired values. When the negative inotropic responses to the anesthetics were compared between groups, analysis of covariance was used and significance was determined by comparison of regression lines (21). A *P* value less than 0.05 was considered significant for all statistical tests.

Results

Body weight, heart weight, and glucose plasma level of streptozotocin-induced diabetic rats that were used in the present study are shown in Table 1 along with values for age-matched control. All diabetic rats were severely hyperglycemic (range 521–1080 mg/dl). Body and heart weights were significantly less in diabetic rats.

As shown in Table 2, there was no difference in the tension development between control and diabetic papillary muscles when the preparations were electrically paced at 0.5 Hz. However, significant differences were observed in the time course of tension development and waning of individual isometric contractions. Thus the time to peak tension and the time for peak-developed tension to decrease to 50% of peak tension (time to ½ relaxation) were significantly prolonged in diabetic muscles (Table 2).

Halothane, enflurane, and isoflurane all produced concentration-dependent negative inotropic effects in control papillary muscles as well as in diabetic ones (Fig. 1). However, the negative inotropic effects of the anesthetics were less in diabetic muscles throughout the range of concentrations used in the present study (Fig. 1). Comparison among the volatile anesthetics of the threshold concentration required to produce a depressant effect on contractile force and the concentration to produce the 50% decrease in developed tension indicated that halothane was the most potent of the three anesthetics in producing the negative inotropic effect, enflurane the least potent, and isoflurane between halothane and enflurane in both control and diabetic papillary muscles. However, diabetic papillary muscles were less sensitive to the negative inotropic effects of the anesthetics than control ones. The concentration of halothane that caused a 50% decrease in developed tension (IC_{50}) was 4.1 ± 0.3 mg/dl in control muscles and 5.6 ± 0.3 mg/dl in diabetic ones, respectively. This difference in IC_{50} between diabetic muscles and control ones was statistically significant ($P < 0.01$). Similarly, the IC_{50} of enflurane and isoflurane significantly increased from 22.4 ± 1.4 and 13.3 ± 1.1 mg/dl in control to 26.6 ± 1.3 ($P < 0.05$) and 19.7 ± 2.3 mg/dl ($P < 0.05$) in diabetic preparations, respectively. Furthermore, comparisons of regression lines (21) showed that decreases in developed tension caused by halothane, enflurane, and isoflurane in diabetic muscles were statistically significantly less than in control muscles (Fig. 2). With each anesthetic, the steepness of the regression line was similar in control and in diabetic muscles, indicating that the developed tension was decreased by a similar extent with a unit increase in anesthetic concentrations in both groups (Fig. 2). However, there was a difference in steepness of the regression line among the anesthetics. Halothane produced the steepest decline in developed tension with increasing concentrations. Isoflurane and enflurane followed halothane in that order.

At the concentrations in which the anesthetics decreased developed tension by approximately 50%, halothane, enflurane and isoflurane significantly abbreviated the time to peak tension and the relaxation time of isometric contractions in both control and diabetic papillary muscles (Table 3).

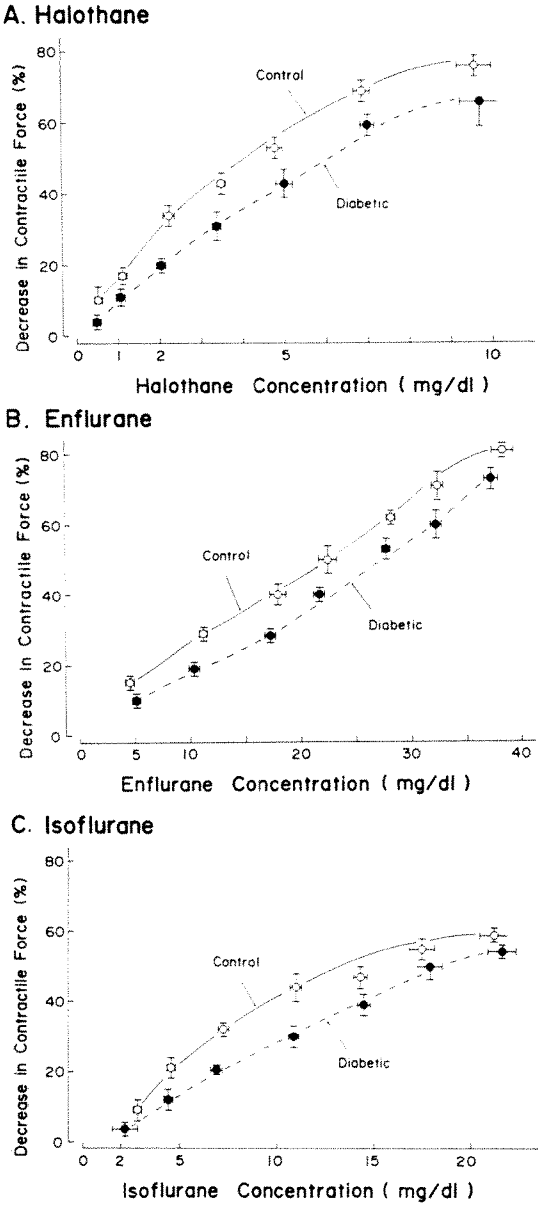

Figure 1. The concentration–response curves for the negative inotropic effects of halothane (**A**), enflurane (**B**) and isoflurane (**C**) in rat papillary muscles from diabetic and control rats. The preparations were constantly stimulated at a frequency of 0.5 Hz. Values are expressed as mean ± SEM. Ten preparations were used in each case.

Discussion

The aim of the present study was to investigate the effects of halothane, enflurane, and isoflurane on the contractile tension of papillary muscles obtained from diabetic rats. In this study diabetes was chemically induced with an injection of streptozotocin (5). The plasma glucose concentration of the streptozotocin-treated rats was nearly 4.5-fold higher than that of the age-matched control ones. Although such severe

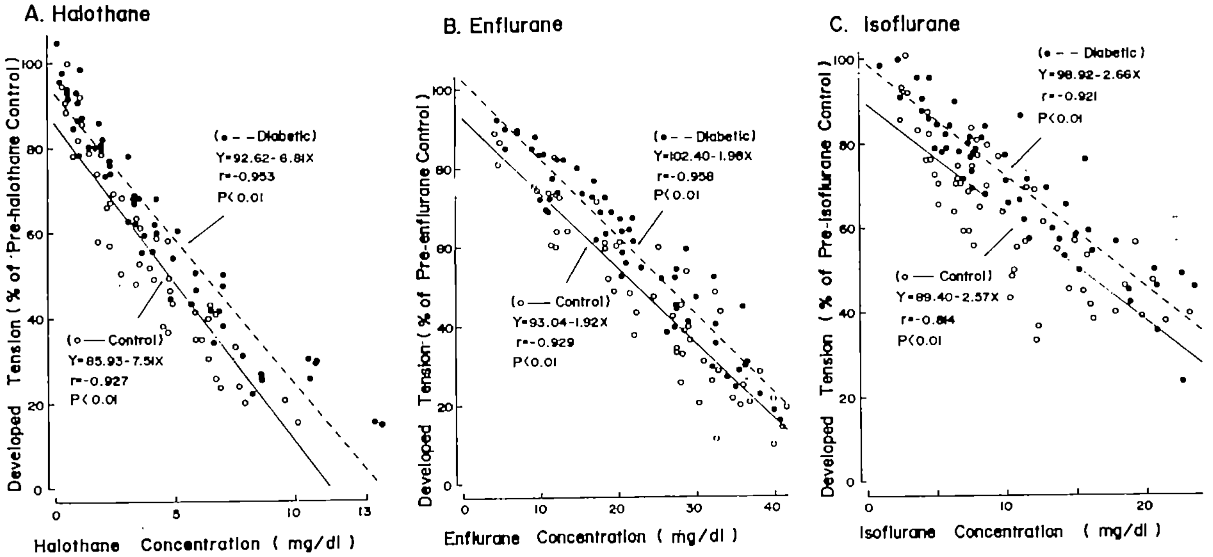

Figure 2. Relationships between the negative inotropic effects and concentrations of halothane (A), enflurane (B) and isoflurane (C) in papillary muscles from diabetic and control rats. The data were described by regression analysis of data presented in Figure 1. Percentages of predrug developed tension are plotted against concentrations of the anesthetics. Note that for any of the anesthetics the slope value of the regression line describing the diabetic data is almost the same as the slope of the control regression line. When comparing the negative inotropic effects of the anesthetics between the two groups, analysis of covariance was used and significance was determined by comparison of regression lines (21).

Table 3. Effects of Halothane, Enflurane, and Isoflurane on Time to Peak Tension and Relaxation Time in Control and Diabetic Papillary Muscles Electrically Paced at 0.5 Hz[a]

	Concentrations of anesthetics (mg/dl)	Time to peak tension (msec)	Time to ½ relaxation (msec)
Control			
None		111 ± 4	67 ± 2
Halothane	4.0 ± 0.2	97 ± 3[b]	62 ± 2[b]
Diabetic			
None		127 ± 4	92 ± 2
Halothane	5.9 ± 0.3	108 ± 3[b]	81 ± 2[b]
Control			
None		100 ± 3	68 ± 1
Enflurane	23.2 ± 1.2	84 ± 2[b]	59 ± 2[b]
Diabetic			
None		126 ± 3	93 ± 5
Enflurane	27.0 ± 1.0	105 ± 3[b]	77 ± 4[b]
Control			
None		99 ± 4	65 ± 2
Isoflurane	14.9 ± 0.6	81 ± 3[b]	55 ± 2[b]
Diabetic			
None		118 ± 2	88 ± 3
Isoflurane	17.9 ± 1.2	97 ± 2[b]	73 ± 2[b]

Results are expressed as mean ± SEM of ten preparations.

[a] In concentrations presented here, all anesthetics produced a decrease in developed tension by around 50% in each case.

[b] $P < 0.001$ vs. the corresponding preanesthetics values. Statistical significance was determined by Student's t-test for paired data.

diabetes resulted in lower body and heart weights in diabetic animals compared with age-matched controls, this malnutrition is known not to be a primary factor in the cardiovascular changes observed in chemically induced diabetic rats (8,22,23). In addition, streptozotocin has been shown not to be cardiotoxic (8). Thus the use of the streptozotocin-diabetic rat has been established as an appropriate experimental model for studying vascular and cardiac dysfunctions in diabetes mellitus.

The results of our present study showed that in the papillary muscle of diabetic rats the negative inotropic effects of halothane, enflurane, and isoflurane are significantly less than in control rats. In fact, the concentrations of the anesthetics that caused a 50% decrease in developed tension were significantly greater in diabetic muscles than those in control ones. These findings suggest a decreased sensitivity of diabetic cardiac muscles to volatile anesthetics. Although for each volatile anesthetic the threshold concentration to produce the negative inotropic effect and the concentration to produce the 50% decrease in developed tension shifted to higher concentrations in diabetic papillary muscles than in control muscles, the relationship between the decrease in developed tension and the bath anesthetic concentrations showed that there was no significant difference in the slope of the regression lines between the control and diabetic papillary muscles. In cat papillary muscles volatile anesthetics have been reported to shorten the time to peak tension and the relaxation time (16,17,20). These findings were confirmed in the present study of rat papillary muscles. Even in diabetic papillary muscles in which the time to peak tension and the relaxation time were significantly prolonged, the volatile anesthetics produced similar shortening of these times. Thus, it seemed unlikely that the action of volatile anesthetics on the excitation–contraction coupling or the contractile machinery in diabetic papillary muscles was different from their action in nondiabetic control muscles.

Although the precise mechanisms whereby volatile anesthetics produce a negative inotropic effect in normal cardiac muscles have not been well elucidated, these anesthetics appear to reduce both the influx of extracellular Ca^{2+} and the amount of Ca^{2+} in the intracellular stores, leading to a decrease in the calcium ions available for the activation of myocardial contractile machinery (24). Because several lines of evidence have suggested that diabetic myocardium has a propensity for developing intracellular Ca^{2+} overload (9,25), it could be inferred that the increased level of myoplasmic Ca^{2+} in diabetic cardiac muscles might compensate for the anesthetic-induced reduction of the amount of calcium ions that participate in the contractile activation. Thus, the alterations in cellular Ca^{2+} dynamics in the diabetic myocardium could counteract the negative inotropic effect exerted by the anesthetics. As an alternative possibility, halothane has been reported to shorten the action potential duration (26) and to reduce the amplitude and the maximum rate of the slow action potential (27) in cardiac muscles, indicating that it inhibits the influx of extracellular Ca^{2+}, perhaps through the voltage-dependent Ca^{2+} channel. Because the action potentials recorded from the diabetic ventricular myocardium are consistently and significantly longer than those of normal ventricular muscle (9,25), the increased action potential duration might partially counteract the inhibition of Ca^{2+} influx induced by the anesthetics.

In conclusion, the negative inotropic effects of halothane, enflurane, and isoflurane are attenuated in papillary muscles obtained from diabetic rats. Although the mechanisms underlying this decreased sensitivity remain obscure at present, it may be due to the result of alterations in the handling of myoplasmic calcium in the diabetic myocardium. Whether these attenuated responses are reversed by insulin is a subject for future investigations.

The authors thank Miss Y. Tsukamoto for her secretarial assistance.

References

1. Kessler I. Mortality experience of diabetic patients. Am J Med 1971;51:715–7.
2. Hamby RI, Zoneraich S, Sherman S. Diabetic cardiomyopathy. JAMA 1974;229:1749–54.
3. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974;34:29–35.
4. Regan TJ, Lyons MM, Ahmed SS, Levinson GE, Oldewurtel HA, Ahmed MR, Haider B. Evidence for cardiomyopathy in familial diabetes mellitus. J Clin Invest 1977;60:885–9.
5. Rerup CC. Drugs producing diabetes through damage of the insulin secreting cells. Pharmacol Rev 1970;22:485–518.
6. Regan TJ, Ettinger PO, Khan MI, Jesrani MV, Lyons MM, Oldewurtel HA, Weber M. Altered myocardial function and metabolism in chronic diabetes mellitus without ischemia in dogs. Circ Res 1974;35:222–37.
7. Penpargkul S, Schaible T, Yipintsoi T, Scheuer J. The effect of diabetes on performance and metabolism of rat hearts. Circ Res 1980;47:911–21.
8. Fein FS, Kornstein LB, Strobeck JE, Capasso JM, Sonnenblick EH. Altered myocardial mechanics in diabetic rats. Circ Res 1980;47:922–33.
9. Fein FS, Aronson RS, Nordin C, Miller-Green B, Sonnenblick EH. Altered myocardial response to ouabain in diabetic rats: mechanics and electrophysiology. J Mol Cell Cardiol 1983;15:769–84.
10. Bloodwell RD, Brown RC, Christensen GR, Goldberg LJ, Morrow AG. The effect of fluothane on myocardial contractile force in man. Anesth Analg 1961;40:352–61.
11. Mahaffey JE, Aldinger EE, Spronse JH, Darby TD, Thrower WB. The cardiovascular effects of halothane. Anesthesiology 1961;22:982–6.
12. Eger EI, Smith NT, Stoelting RK, Cullen DJ, Kadis LB, Whitcher CE. Cardiovascular effects of halothane in man. Anesthesiology 1970;32:396–409.
13. Asher M, Frederickson EL. Halothane versus chloroform: the dose response using the isolated rabbit heart. Anesth Analg 1962;41:429–34.
14. Goldberg AH, Ullrick WC. Effects of halothane on isoelectric contractions of isolated heart muscle. Anesthesiology 1967;28:838–45.

15. Brown BR, Crout JR. A comparative study of the effects of five general anesthetics on myocardial contractility: I. Isometric conditions. Anesthesiology 1971;34:236–45.
16. Kemmotsu O, Hashimoto Y, Shimosato S. The effects of fluroxene and enflurane on contractile performance of isolated papillary muscles from failing hearts. Anesthesiology 1974;40:252–60.
17. Kemmotsu O, Hashimoto Y, Shimosato S. Inotropic effects of isoflurane on mechanics of contraction in isolated cat papillary muscles from normal and failing hearts. Anesthesiology 1973;39:470–7.
18. Lowenstein E, Foex P, Francis M, Davies WL, Yusuf S, Ryder WA. Regional ischemic ventricular dysfunction in myocardium supplied by a narrowed coronary artery with increasing halothane concentration in dog. Anesthesiology 1981;55:349–59.
19. Kissin I, Thomson CT, Smith LR. Effect of halothane on contractile function of ischemic myocardium. J Cardiovasc Pharmacol 1983;5:438–42.
20. Shimosato S, Yasuda I, Kemmotsu O, Shanks C, Gamble C. Effect of halothane on altered contractility of isolated heart muscle obtained from cats with experimentally produced ventricular hypertrophy and failure. Br J Anaesth 1973;45:2–9.
21. Snedecor GW, Cochran WG. Statistical methods. 6th ed. Ames, Iowa: The Iowa State University Press, 1967:419–46.
22. Cohen EM, Abelmann WH, Messer JV, Bing OHL. Mechanical properties of rat cardiac muscle during experimental thiamine deficiency. Am J Physiol 1976;231:1390–4.
23. Longhurst PA, Head RJ. Responses of the isolated perfused mesenteric vasculature from diabetic rats: the significance of appropriate control tissues. J Pharmacol Exp Ther 1985;235:45–9.
24. Komai H, Rusy BF. Differences in the myocardial depressant action of thiopental and halothane. Anesth Analg 1984;63:313–8.
25. Nordin C, Gilat E, Aronson RS. Delayed afterdepolarization and triggered activity in ventricular muscle from rats with streptozotocin-induced diabetes. Circ Res 1985;57:28–34.
26. Hauswirth O. Effects of halothane on single atrial, ventricular, and Purkinje fibers. Circ Res 1969;26:745–50.
27. Lynch C III, Vogel S, Sperelakis N. Halothane depression of myocardial slow action potentials. Anesthesiology 1981;55:360–8.

Negative Inotropic Effects of Isoflurane and Halothane in Rabbit Papillary Muscles

Hirochika Komai, PhD, and Ben F. Rusy, MD

KOMAI H, RUSY BF. Negative inotropic effects of isoflurane and halothane in rabbit papillary muscles. Anesth Analg 1987;66:29–33.

The possibility that the negative inotropic effect of isoflurane is primarily due to a competitive inhibition of the influx of extracellular Ca^{2+} with little effect on the availability of Ca^{2+} stored intracellularly in the sarcoplasmic reticulum was examined in rabbit papillary muscle. The negative inotropic effect of isoflurane (1.4%) on steady state contractions (primarily dependent on the influx of extracellular Ca^{2+}) was significantly greater than that on potentiated-state contractions (primarily dependent on Ca^{2+} released from the sarcoplasmic reticulum). In previous work from this laboratory we found that halothane has an opposite effect in this regard. Increasing stimulation frequency in the presence of isoproterenol (0.1, 1 μM) completely reversed the negative inotropic effect of isoflurane (1.4%) but not that of halothane (0.6%). These results suggest that isoflurane inhibits Ca^{2+} influx with little effect on the availability of activator Ca^{2+} stored in and released from the sarcoplasmic reticulum, and that the effect of isoflurane but not that of halothane can be effectively counteracted by conditions that are known to increase Ca^{2+} influx in the absence of an anesthetic. These properties of isoflurane may in part account for the minimal myocardial depressant effect of the anesthetic on the intact heart in the presence of a functional autonomic system.

Key Words: ANESTHETICS, VOLATILE—isoflurane, halothane. HEART—contractility.

The myocardial depressant effect of isoflurane appears to be less than that of halothane in intact animal models (1), even though the negative inotropic effect of isoflurane is comparable to that of halothane in isolated myocardial preparations (2). A possible reason for this discrepancy is that the negative inotropic effect of isoflurane in the intact heart can be effectively reversed by sympathetic nervous activity. For this reason, we have examined the possibility that the negative inotropic effect of isoflurane is primarily due to the inhibition of Ca^{2+} influx across the sarcolemma with little effect on the availability of intracellularly stored Ca^{2+} and that the mode of inhibition is such that it can be effectively counteracted by interventions that increase the Ca^{2+} influx. Activation of myocardial contractile activity is dependent on the influx of extracellular Ca^{2+} and on the release of intracellularly stored Ca^{2+} (3), and the relative contribution of Ca^{2+} from these sources varies depending on stimulation conditions. For example, ryanodine (a specific inhibitor of the release of Ca^{2+} intracellularly stored in the sarcoplasmic reticulum) (4) inhibits potentiated-state contractions with much less effect on steady state contractions at high stimulation frequencies (5). This indicates that the contribution of the intracellularly stored Ca^{2+} is more important in the potentiated-state contraction than in the steady state contraction. Accordingly, a comparison of the effects of isoflurane on potentiated-state contractions and steady state contractions should provide information concerning the relative effects of isoflurane on the availability of extracellular and intracellular Ca^{2+}. To test the possibility that isoflurane competitively inhibits the influx of extracellular Ca^{2+}, we have examined the effect of increased stimulation frequency in the presence of a high concentration of isoproterenol, a condition known to maximize Ca^{2+} influx as well as the force of contraction in the absence of an anesthetic.

Materials and Methods

Rabbits weighing about 2 kg were anesthetized by intravenous injection of pentobarbital (approximately 45 mg/kg). The heart was excised and a papillary mus-

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This study was supported in part by the National Institutes of Health Grant GM 29527 and by a grant-in-aid from the University of Wisconsin, Department of Anesthesiology Research and Development fund. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, October 1985, San Francisco, California.

Received from the Department of Anesthesiology, Center for Health Sciences, University of Wisconsin, Madison, Wisconsin. Accepted for publication August 4, 1986.

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Table 1. Negative Inotropic Effect of Isoflurane, Ni^{2+}, and Ryanodine on the Steady State Contractions at a Stimulation Frequency of 2.0 Hz and in Potentiated-State Contractions Elicited after 2 sec of Rest after the Steady State at 2.0 Hz Stimulation

	Percent inhibition		
Addition	Steady state	Potentiated state	*P* value
1.1% isoflurane (*n* = 6)	29 ± 3	26 ± 2	ns
1.4% isoflurane (*n* = 8)	40 ± 3	36 ± 3	<0.01
2 mM Ni^{2+} (*n* = 11)	52 ± 5	45 ± 5	<0.01
1 μM ryanodine (*n* = 8)	27 ± 4	69 ± 1	<0.01

Means ± SEM are shown. The statistical significance of the difference between the inhibitory effects in the two contractile states was evaluated by paired *t*-test.

Abbreviation: ns, not significant.

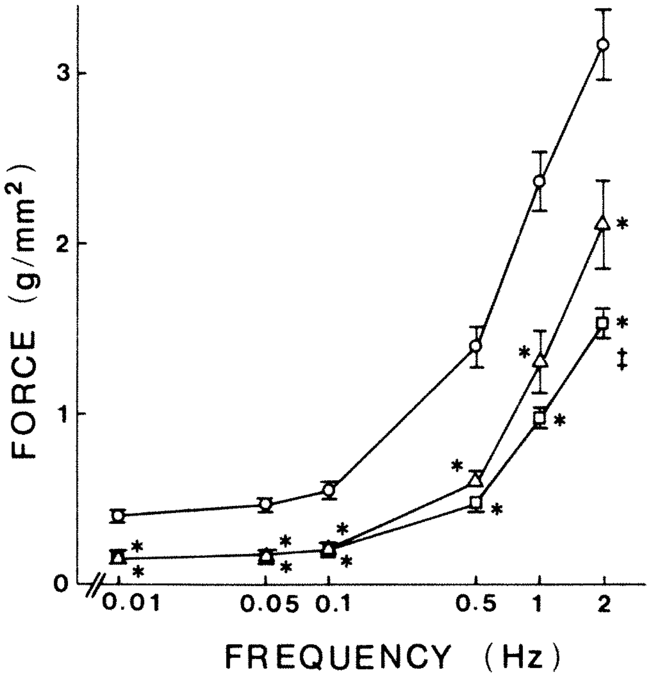

Figure 1. Negative inotropic effects of isoflurane and halothane at different stimulation frequencies. Means ±SEM are shown. The effects of anesthetics at each stimulation frequency were compared by unpaired *t*-test. ○, Control (*n* = 24); △, +1.4% isoflurane (*n* = 12); □, +0.6% halothane (*n* = 12). *$P < 0.01$, compared with control; ‡$P < 0.05$, +0.6% halothane compared to +1.4% isoflurane.

cle was isolated from the right ventricle. The average cross-sectional area of the 41 muscles so obtained was 0.75 ± 0.17 mm^2 (SD). The muscle was mounted vertically in a tissue bath (45 ml) maintained at 30°C. The lower end of the muscle was tied to a fixed base and the upper end to a stainless steel wire attached to a Statham UC-2 force transducer mounted on a micrometer for the adjustment of resting tension. Isometric developed force was recorded on a Gilson polygraph. The cross-sectional areas of the muscles were obtained from measurements of muscle diameter by an ocular micrometer using a Unitron binocular microscope. The resting tension was maintained at 1 g throughout the experiments. The stimuli (4 msec duration, 1.5 × threshold) were delivered through silver–silver chloride field electrodes. A Laboratory Stimulator (American Electronic Laboratories, model 104A) was used. The medium used was a modified Krebs–Henseleit bicarbonate (pH 7.4) of the following composition: NaCl, 115 mM; KCl, 5.9 mM; $MgCl_2$, 1.2 mM; NaH_2PO_4, 1.2 mM; Na_2SO_4, 1.2 mM; $NaHCO_3$, 25 mM; $CaCl_2$, 2.5 mM; ethylenediamine tetraacetate (EDTA), 50 μM (for chelation of trace metals); and glucose, 5.6 mM. The medium was equilibrated with a gas mixture of 95% O_2 and 5% CO_2. Isoflurane and halothane were added to the above gas mixture using Dräger vaporizers calibrated by gas chromatography. Concentrations of anesthetics used (isoflurane 1.4%, halothane 0.6%) were those that were determined by preliminary experiments to inhibit the force of contraction to about 50% under the basal condition (low stimulation frequency, absence of isoproterenol). Anesthetic concentrations in the medium as determined by extraction (6) were 0.37 mM for isoflurane and 0.16 mM for halothane. Potentiated state contractions were elicited by stimulating the muscle after 2 sec of rest after interruption of a train of steady state contractions at 2.0 Hz (7). In the first series of the experiments, effects of one or two drugs were tested with each muscle. When two different drugs were used, a 30 min washout with the drug-free medium preceded the addition of the second drug. Because the effect of ryanodine is not readily reversed by washout, ryanodine was never used as the first of the two drugs to be tested. In the second series of experiments, the effects of either isoflurane or halothane were studied after the control measurements, followed by the effects of isoproterenol plus the anesthetic, and finally the effects of isoproterenol alone after removal of the anesthetic. Ten to thirty minutes were allowed for the stabilization of the force of contraction after each change in the composition of the medium before measurements were made, and the total duration of exposure of the muscle to each drug was 0.5–1 hr. After isolation the muscles were allowed to contract at a frequency of 0.1 Hz for a period of 2–3 hr in order to effect stabilization. After this the muscles remained stable for a period of 3–4 hr during which the experiments were performed. Data were analyzed statistically by Student's paired or unpaired *t*-test as indicated. *P* less than 0.05 was considered statistically significant.

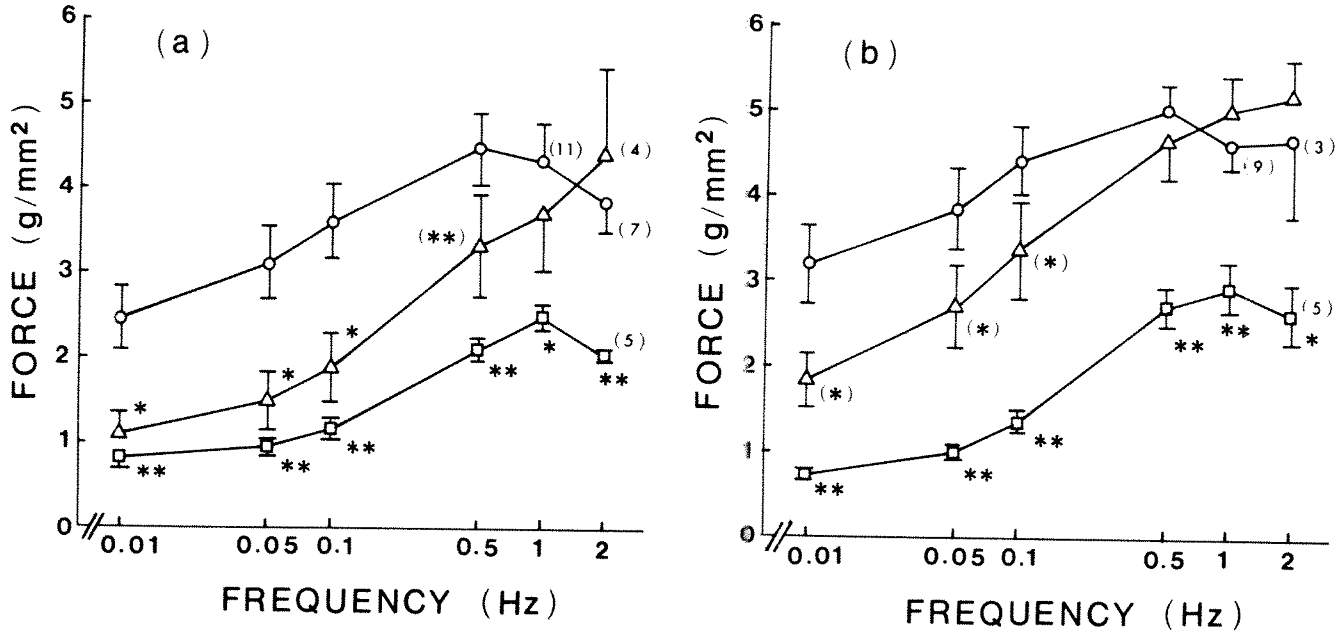

Figure 2. **(a,b)**. Effect of isoflurane and halothane at different stimulation frequencies in the presence of isoproterenol. Isoproterenol concentration: **(a)**, 0.1 μM; and **(b)**, 1 μM. Means ± SEM are shown. ○, No anesthetic; △, 1.4% isoflurane; □, 0.6% halothane. Numbers of muscles were 12, 6, and 6 respectively for no anesthetic, isoflurane, and halothane, unless indicated otherwise in parentheses. $^*P < 0.05$, $^{**}P < 0.01$, compared with corresponding "no anesthetic" value (unpaired *t*-test). (*), $P < 0.05$; (**), $P < 0.01$, when comparison was made with corresponding "no anesthetic" value of the same muscle and evaluated by paired *t*-test ($n = 6$) but not significant when evaluated by unpaired *t*-test.

Results

The inhibitory effect of isoflurane (1.4%) on potentiated-state contractions was significantly less ($P < 0.01$, paired *t*-test) than that on the preceding, steady state contractions (Table 1). The difference was not significant with a lower concentration of isoflurane (1.1%). Table 1 also shows the effects of Ni^{2+} and of ryanodine for comparison. Nickel ion is an inhibitor of the influx of extracellular Ca^{2+} through the slow channel (8), whereas ryanodine is a specific inhibitor of Ca^{2+} release from the sarcoplasmic reticulum (4). It should be noted that an inhibition of Ca^{2+} influx most likely reduces the amount of Ca^{2+} stored intracellularly. For this reason, even if an agent is a relatively specific inhibitor of Ca^{2+} influx the difference in its effect on potentiated-state contractions as compared with that on steady state contractions is not as pronounced as that found with ryanodine, which inhibits Ca^{2+} release from the sarcoplasmic reticulum but has no inhibitory effect on Ca^{2+} influx (9).

As can be seen in Figure 1, isoflurane and halothane significantly ($P < 0.01$) inhibited the force of contraction at all stimulation frequencies tested. At 2.0 Hz, but not at lower frequencies, the inhibitory effect of isoflurane was significantly ($P < 0.05$) less than that of halothane (Fig. 1). A similar result was reported by Lynch (10) with 1.3% isoflurane and 0.75% halothane in guinea pig papillary muscles. The difference between isoflurane and halothane was more pronounced when the two anesthetics were compared in the presence of two concentrations of isoproterenol (Fig. 2). Although the effects of isoflurane and halothane were indistinguishable at low stimulation frequencies in the presence of 0.1 μM isoproterenol, an increase in stimulation frequency or an increase in the concentration of isoproterenol to 1 μM markedly reduced the negative inotropic effect of isoflurane but not that of halothane, as the latter persisted even in the presence of 1 μM isoproterenol. Stimulation of the muscles at high frequencies in the presence of isoproterenol often induced spontaneous contractile activity, precluding the determination of the force of contraction. This accounts for the fewer number of muscles in the data points at high stimulation frequencies in the presence of isoproterenol.

Discussion

The finding that isoflurane inhibition of potentiated-state contractions was significantly less than that of steady-state contractions strongly suggests that isoflurane's effect on the availability of Ca^{2+} stored in and released from the sarcoplasmic reticulum is not primarily responsible for the negative inotropic effect of the anesthetic. In this regard, isoflurane resembles Ni^{2+} (an inhibitor of Ca^{2+} influx) (8) and is different from ryanodine (a specific inhibitor of Ca^{2+} release from the sarcoplasmic reticulum) (4). In addition to the nickel ion (11,12), other ions and compounds that reduce the influx of extracellular Ca^{2+}, such as Co^{2+} (11), D600 (13), and the lowering of the extracellular Ca^{2+} concentration (14), are also known to have less effect on potentiated-state contractions than on steady state contractions. Earlier we found that the negative inotropic effect of halothane on potentiated-state contractions was significantly *greater* than that on steady state contractions (7). Thus it appears very likely that the effect of isoflurane on the function of the sarcoplasmic reticulum is less than that of halothane. Our results are consistent with those of Su et al. (15,16), who found isoflurane to have less inhibitory effect than halothane on a caffeine-induced tension transient considered to be due to Ca^{2+} stored in and released from the sarcoplasmic reticulum. In contrast, Lynch (10) has suggested that isoflurane's effect on Ca^{2+} influx contributes little to the negative inotropic effect of the anesthetic, based in part on his finding that isoflurane has a pronounced effect on the late peak of biphasic rested-state contractions that Reiter et al. (17) proposed are activated by Ca^{2+} released internally from the sarcoplasmic reticulum. It is important to note that typical inhibitors of the function of sarcoplasmic reticulum such as caffeine, theophylline, and ryanodine inhibit the force of contraction of the early but not the late peaks of biphasic contractions generated under a variety of conditions with various myocardial preparations (18–21). In fact, the force of contraction of the *late* peak is inhibited by inhibitors of Ca^{2+} influx such as nifedipine (17), verapamil (18), and Mn^{2+} (21), indicating that extracellularly derived Ca^{2+} is involved.

The observed mode of reversal of the negative inotropic effect of isoflurane by isoproterenol further suggests that isoflurane competitively inhibits Ca^{2+} influx. In contrast, we have shown that the negative inotropic effect of halothane persists even in the presence of a high concentration of isoproterenol. Note that Iwatsuki and Iwatsuki found that increasing stimulation frequency (22), addition of dibutyryl cAMP (23), and increasing extracellular Ca^{2+} concentration (24) were not as effective in reversing the negative inotropic effect of halothane as they were in reversing the effect of thiamylal. Our results with halothane are in agreement with those of Iwatsuki and Iwatsuki (22–24). In contrast, Price (25) reported that halothane's effect is competitive with extracellular Ca^{2+}. Although we cannot explain the difference between our results and those of Price, it remains that the effect of halothane persisted even in the presence of the highest concentration of Ca^{2+} used by Price (25). Although isoproterenol may enhance the ability of the sarcoplasmic reticulum to accumulate Ca^{2+} (26), the observed ability of the combination of isoproterenol and an increased stimulation frequency to overcome the negative inotropic effect of isoflurane is difficult to explain in terms of the effects on Ca^{2+} content of the sarcoplasmic reticulum, because Ca^{2+} stored in and released from the sarcoplasmic reticulum plays only a minor role in contractions at high stimulation frequencies (5).

In conclusion, the results of the present study strongly suggest the following: 1) that isoflurane and halothane inhibit the influx of extracellular Ca^{2+} and that the effect of isoflurane but not that of halothane can be effectively counteracted by conditions that are known to increase Ca^{2+} influx in the absence of an anesthetic, and 2) the effect of isoflurane to inhibit the function of the sarcoplasmic reticulum is most likely less than that of halothane.

Ryanodine was a generous gift of Dr. L. R. Jones.

References

1. Merin RG. Are the myocardial functional and metabolic effects of isoflurane really different from those of halothane and enflurane? Anesthesiology 1981;55:398–408.
2. Kemmotsu O, Hashimoto Y, Shimosato S. Inotropic effects of isoflurane on mechanics of contraction in isolated cat papillary muscles from normal and failing hearts. Anesthesiology 1973;39:470–7.
3. Morad M, Goldman Y. Excitation-contraction coupling in heart muscle: membrane control of development of tension. Prog Biophys Mol Biol 1973;27:257–313.
4. Sutko JL, Kenyon JL. Ryanodine modification of cardiac muscle responses to potassium-free solutions. Evidence for inhibition of sarcoplasmic reticulum calcium release. J Gen Physiol 1983;82:385–404.
5. Sutko JL, Willerson JT, Templeton GH, Jones LR, Besch HR Jr. Ryanodine: Its alterations of cat papillary muscle contractile state and responsiveness to inotropic interventions and a suggested mechanism of action. J Pharmacol Exp Ther 1979;209:37–47.
6. Fink BR, Morikawa K. A simplified method for the measurement of volatile anesthetics in blood by gas chromatography. Anesthesiology 1970;32:451–5.
7. Komai H and Rusy BF. Differences in the myocardial depressant action of thiopental and halothane. Anesth Analg 1984;63:313–8.
8. Kohlhardt M, Bauer B, Krause H, Fleckenstein A. Selective inhibition of the transmembrane Ca conductivity of mammalian myocardial fibers by Ni, Co and Mn ions. Pflügers Arch 1973;338:115–23.
9. Mitchell MR, Powell T, Terrar DA, Twist VW. Ryanodine prolongs Ca-currents while suppressing contraction in rat ventricular muscle cells. Br J Pharmacol 1984;81:13–5.

10. Lynch C III. Differential depression of myocardial contractility by halothane and isoflurane in vitro. Anesthesiology 1986;64:620–31.

11. Bass O. The decay of the potentiated state in sheep and calf ventricular myocardial fibers. Influence of agents acting on transmembrane Ca^{2+} flux. Circ Res 1976;39:396–9.

12. Lewartowski B, Prokopezuk A, Pytkowski B. Effect of inhibitors of slow calcium current on rested state contraction of papillary muscles and post rest contractions of atrial muscle of the cat and rabbit heart. Pflügers Arch 1978;377:167–75.

13. Willerson JT, Crie S, Adcock RC, Templeton GH, Wildenthal K. Influence of calcium on the intropic actions of hyperosmotic agents, norepinephrine, paired electrical stimulation, and Treppe. J Clin Invest 1974;54:957–64.

14. Penna M, Garb S. Relationship of changes in ionic concentrations to the augmentation produced by extra contractions in isolated mammalian ventricular muscle. Am J Physiol 1956;184:572–4.

15. Su JY, Kerrick GL. Effects of halothane on caffeine-induced tension transients in functionally skinned myocardial fibers. Pflügers Arch 1979;380:29–34.

16. Su JY, Bell JG. Intracellular mechanism of action of isoflurane and halothane on striated muscle of the rabbit. Anesth Analg 1986;65:457–62.

17. Reiter M, Vierling W, Seibel K. Excitation-contraction coupling in rested-state contractions of guinea-pig ventricular myocardium. Naunyn Schmiedebergs Arch Pharmacol 1984;325:159–69.

18. Bogdanov KY, Zakharov SI, Rosenshtraukh LV. The origin of two components in contraction of guinea pig papillary muscle in the presence of noradrenaline. Can J Physiol Pharmacol 1979;57:866–72.

19. Honerjäger P, Greger R, Hammersen F. Ryanodine alters cardiac contraction without detaching the sarcolemma from couplings. Naunyn Schmiedebergs Arch Pharmacol 1979;308:R36.

20. Endoh M, Iijima T, Motomura S. Inhibition by theophylline of the early component of canine ventricular contraction. Am J Physiol 1982;242:H349–H58.

21. King B, Bose D. Mechanism of biphasic contractions in strontium-treated ventricular muscle. Circ Res 1983;52:65–75.

22. Iwatsuki N, Iwatsuki K. Effects of change in frequency of stimulation on myocardial depression produced by thiamylal and halothane. Tohoku J Exp Med 1975;117:110–24.

23. Iwatsuki N, Iwatsuki K. Effects of dibutyryl cyclic AMP on contractile performance of isolated heart muscle depressed by thiamylal and halothane. Tohoku J Exp Med 1974;113:357–63.

24. Iwatsuki N, Iwatsuki K. Effects of changes in concentration of calcium on myocardial contractility depressed by thiamylal and halothane. Tohoku J Exp Med 1976;120:1–9.

25. Price HL. Calcium reverses myocardial depression caused by halothane. Anesthesiology 1974;41:576–9.

26. Hunter DR, Haworth RA, Berkoff HA. Modulation of cellular calcium stores in the perfused rat heart by isoproterenol and ryanodine. Circ Res 1983;53:703–12.

Effect of Epidural Bupivacaine on Somatosensory Evoked Potentials after Dermatomal Stimulation

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LUND C, SELMAR P. HANSEN OB, HJORTSØ N-C, KEHLET H. Effect of epidural bupivacaine on somatosensory evoked potentials after dermatomal stimulation. 1987;66:34–8.

The effect of lumbar epidural analgesia with plain bupivacaine, 0.5%, on early (<0.5 sec) somatosensory evoked potentials (SEP) to electrical stimulation of the T-10, L-1, and S-1 dermatomes and the posterior tibial nerve was examined in eight patients. A decrease of the cortical amplitude and an increase in latency were seen, most pronounced at the L-1 level, but with only minor effect on the S-1 dermatome. No correlation was found between segmental level of analgesia and decrease in amplitude of the evoked potentials. Thus despite clinically adequate surgical anesthesia, the neural pathways as assessed by SEP were incompletely blocked except at the L1 dermatome near the epidural injection site.

Key Words: ANESTHETIC TECHNIQUES—epidural
BRAIN—evoked potentials.

Neural blockade by epidural administration of local anesthetics is a well-established technique to achieve analgesia in the perioperative period. The extent of the blockade may be evaluated by careful neurological examination with assessment of analgesia by pin prick, loss of temperature discrimination, and touch (1). However, different local anesthetic agents may have differential effect on different nerve fibers (2,3), and these discrepancies may be difficult to assess.

Measuring somatosensory evoked potentials (SEPs), defined as changes in the electroencephalogram after somatosensory stimulation, recorded using computer averaging technique (4), is an accepted method for objective assessment of the integrity of sensory pathways and has been used in pain research (5–8). These studies have shown that the intensity of peripheral painful somatic stimulation correlates with the amplitude of the cortical SEPs and that subjectively evaluated pain increases linearly with evoked potential amplitudes (9,10). Inhalational anesthetics, opiates, and sedatives have been shown to reduce the amplitude of evoked potentials (11–15), whereas there is a lack of sufficient information on the influence of neural blockade by local anesthetics on SEP (16,17). The aim of our study was to investigate the effects of lumbar epidural analgesia with bupivacaine on cortical SEP after cutaneous electrical stimulation within the region of the nerve block.

Methods

Patients

Eight patients, two women and six men, mean age 34 yr (range 20–59 yr), were studied. None had symptoms, signs, or history of neuromuscular disease. All were admitted to the hospital for elective abdominal surgery that justified use of an epidural catheter for management of postoperative pain. The declaration of Helsinki was respected, and informed consent was obtained from all patients.

Stimulation

Electrical stimuli lasting 0.2 msec were applied via a bipolar surface electrode (DANTEC/DISA 13 L 22, Copenhagen, Denmark) at a rate of 1.5 stimuli/sec. The stimulation electrode covered 7 × 30 mm. Four unilateral areas were stimulated posterior to the medial malleolus of the ankle at an intensity of 1.5 times the motor threshold (TM). The TM of the posterior tibial nerve (PTN) was the intensity just able to elicit a motor response in the flexor muscles of the toes. The

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Received from the Departments of Anesthesiology and Surgical Gastroenterology, Hvidovre University Hospital, Hvidovre, Denmark, and the Department of Clinical Neurophysiology, Glostrup Hospital, Glostrup, Denmark. Accepted for publication August 21, 1986.

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Table 1. Influence of Epidural Bupivacaine on Amplitude of Components of the Early Somatosensory Evoked Cortical Potentials after Stimulation of the Posterior Tibial Nerve and the S-1, L-1, and T-10 Dermatomes.

	SEP amplitude (μV)[a]											
	PTN			S-1			L-1			T-10		
	Before	During	P	Before	During	P	Before	During	P	Before	During	P
P_1	3.3 ± 0.8	2.0 ± 0.6	<0.004	1.9 ± 0.4	2.1 ± 0.8	ns	1.4 ± 0.3	0.4 ± 0.1	<0.009	1.2 ± 0.4	0.4 ± 0.1	<0.05
N_1	3.4 ± 0.8	2.7 ± 0.9	ns	3.6 ± 0.8	4.5 ± 2.0	ns	2.2 ± 0.5	0.6 ± 0.2	<0.006	1.7 ± 0.9	0.6 ± 0.2	ns
P_2	2.4 ± 0.9	2.4 ± 0.8	ns	2.8 ± 0.8	2.7 ± 0.6	ns	2.8 ± 1.1	0.5 ± 0.2	<0.02	1.8 ± 0.9	0.5 ± 0.2	ns
N_2	4.9 ± 1.3	4.4 ± 1.4	ns	1.8 ± 0.5	2.7 ± 0.8	ns	2.1 ± 0.6	0.6 ± 0.1	<0.01	0.9 ± 0.2	0.6 ± 0.1	ns
P_3	3.0 ± 0.7	3.1 ± 1.1	ns	5.1 ± 2.9	3.2 ± 0.8	ns	1.2 ± 0.3	0.4 ± 0.2	<0.04	0.7 ± 0.2	0.4 ± 0.2	ns
N_3	—	—	—	—	—	—	1.3 ± 0.4	0.7 ± 0.2	<0.03	1.3 ± 0.4	0.7 ± 0.2	<0.05
Peak to peak	4.9 ± 1.0	4.6 ± 1.4	ns	4.8 ± 0.8	3.7 ± 0.9	<0.02	3.4 ± 0.7	0.6 ± 0.2	<0.006	2.7 ± 0.7	1.0 ± 0.2	<0.02

Abbreviations: PTN, posterior tibial nerve; ns, not significant.
[a]Mean ± SEM.

sensory sural nerve, which mainly innervates the area of the S-1 dermatome, was stimulated posterior to the lateral malleolus of the ankle. The cutaneous sensory nerves of the L-1 and T-10 dermatomes were stimulated at the anterior superior iliac spine and in the midline just inferior to the umbilicus, respectively.

The three sensory areas were stimulated at an intensity of four times the sensory threshold (TS). TS was defined as the midpoint between the stimulus intensity needed for just-detectable perception of stimulation and for just-detectable loss of perception of stimulation. Direct stimulation of muscles in the latter three areas was avoided. Stimulation before institution of epidural analgesia resulted in tolerable pain. The procedure was repeated after establishment of epidiural analgesia (see below).

Recording

The cortical activity was recorded from platinum needle electrodes (DANTEC/DISA 25 C 04) at the midline of the scalp, 2 cm posterior and 5 cm anterior (reference) to the vertex located C_z of the International 10–20 system for EEG recording. During each stimulation procedure 1000 responses were averaged. A DANTEC/DISA Neuromatic 2000 neuro-myograph was used for stimulation and recording. The amplifier had a bandpass (−3 dB) of 0.5–1000 Hz; the analysis time was 500 msec. The recorded cortical evoked potentials were analyzed. The latency of the onset (O) and the first positive (P_1–P_3) and negative (N_1–N_3) peaks were measured, as were the peak-to-peak amplitudes.

Epidural Analgesia

A lumbar (L2–3) epidural catheter was inserted and 26.9 ± 1.5 ml (mean ± SEM) plain 0.5% bupivacaine was injected. SEP recordings were made before insertion of the epidural catheter and when maximal spread of sensory analgesia (bilateral pin prick) was achieved (47 ± 2 min, mean ± SEM). All recordings were performed before surgery.

Statistics

Changes in SEP were assessed by Student's t-test for paired data and linear correlations between extent of analgesia and degree of motor blockade versus changes in SEP were calculated by the methods of least squares. $P < 0.05$ was considered statistically significant.

Results

Mean level of analgesia (pin prick) was T-6.8 ± 0.9 (mean ± SEM) and mean degree of motor blockade was 1.6 ± 0.5 according to the Bromage scale from 1 to 4 (1 = full paralysis, 4 = none) (18).

During epidural analgesia, a significant reduction of the peak-to-peak amplitude of the S-1, L-1 and T-10 SEP potentials was found. Likewise, the P-1 amplitude of the PTN decreased (Table 1). The most pronounced changes were seen at the L1 level, where every peak (N1–3, P1–3) decreased significantly. Figure 1 shows the mean SEP potentials before and during blockade. The effect of epidural bupivacaine was most pronounced at L1, where SEP potentials were abolished in four of the eight patients. The latency of the early SEP components increased significantly at S-1, L-1, and T-10. The effect was most consistent at L-1 (Table 2). Figure 2 shows the change in P-1 latency during blockade ($P < 0.05$ at all stimulation sites except PTN). The sensory thresholds (TS) increased significantly at L-1 and T-10 during neural blockade, but insignificantly at the S-1 level (Fig. 3).

No correlation was found between the dermatomal level of analgesia and the block-induced decrease in the dermatomal evoked potential amplitudes ($r < 0.7$, $P > 0.1$), or between the degree of motor blockade and the change in SEP amplitude after stimulation of the PTN ($r < 0.5$, $P > 0.1$).

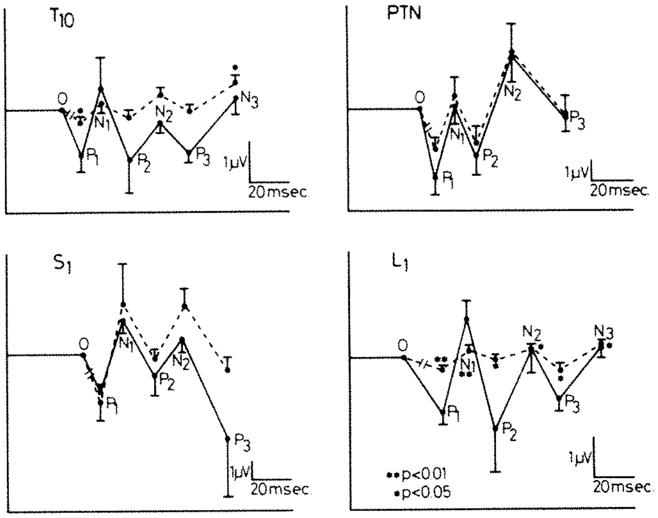

Figure 1. Mean cortical somatosensory evoked potentials before and during epidural blockade with bupivacaine, 0.5%, elicited by stimulation at four stimulation sites (see text). Solid line, before blockade; dashed line, during blockade ($n = 8$, values are mean ± SEM). The change of latency is not shown in this figure.

Discussion

The results of our study show that the amplitudes and the latencies of the SEP components within latencies of 200 msec were susceptible to epidural blockade with bupivacaine. To our knowledge, this has been previously demonstrated only in one preliminary clinical study (17), where a minor reduction of SEP amplitude and prolonged latency to posterior tibial nerve stimulation were found. In experimental studies in monkeys, epidural injection of 0.5% bupivacaine also reduced SEP amplitude elicited by electrical stimulation (2). In our study with a mean level of analgesia of T-6.8 and a pronounced motor blockade, we found a reduction of the amplitude of all peaks after stimulation of L-1 dermatome, but only peak-to-peak when stimulating S-1, and in P-1, N-3, and peak-to-peak when stimulating T-10. The block only reduced P-1 after stimulation of the PTN. SEP was abolished in four of eight patients when stimulated at the L-1 level and in two patients at the T-10 level. Despite the minor influence on amplitude after S-1 stimulation at the onset, P-1 and N-1 latency increased significantly. PTN stimulation latency was unaltered by the block except for an increased onset time. The SEP changes after PTN stimulation during blockade are in accordance with previous studies (17). We found no correlation between the level of analgesia and reduction of the SEP amplitude. At the T-10 and L-1 level, where the block induced the most pronounced changes, we found a significantly increased sensory threshold, but no change at S-1 level. The demonstrated relative resistance to local anesthetics at the S-1 level, as found by SEP, is in accordance with the clinical experience that epidural analgesia is often inadequate for surgery in this area (19). The explanation of this phenomenon is unknown. Concerning the dermatomal sensory nerve stimulation, the most pronounced changes were seen after stimulation of the L-1 dermatome. This may be due to higher concentrations of the local anesthetic agent at this level, because the injection site was L2–3. When stimulating at the T-10 level, we found only partial amplitude changes, indicating that nerve signals were able to pass through a presumably blocked area as assessed by pin prick. This may explain why the endocrine metabolic response to major abdominal surgery may only be partially modified by epidural analgesia despite acceptable pain relief (20), in contrast to the pronounced reduction in the stress response by epidural analgesia in lower abdominal (gynecologic) procedures (20). However, further studies on SEP during thoracic epidural bupivacaine are needed to clarify this point.

We found no correlation between the degree of motor blockade and the evoked potentials elicited by stimulation of the PTN, which is a mixed sensory motor nerve. The explanation may be that the stimulated area is innervated by sensory nerve fibers from L-4, L-5, and S-1 and that the S-1 pathway is insufficiently blocked as mentioned above.

Table 2. Influence of Epidural 0.5% Bupivacaine on Latency of the Onset and the First Three Positive–Negative Peaks of the Somatosensory Evoked Cortical Potentials[a]

	SEP latency (msec)[b]							
	PTN		S-1		L-1		T-10	
	Before	*P*	Before	*P*	Before	*P*	Before	*P*
Onset	36.2 ± 2	<0.025	38 ± 2	<0.025	25 ± 2	<0.01	28 ± 1	<0.005
P_1	43 ± 1	ns	46 ± 1	<0.025	34 ± 2	<0.005	37 ± 2	<0.025
N_1	63 ± 2	ns	57 ± 2	<0.025	45 ± 2	<0.005	47 ± 2	<0.025
P_2	63 ± 2	ns	72 ± 3	ns	59 ± 3	<0.01	60 ± 1	ns
N_2	81 ± 3	ns	87 ± 2	ns	77 ± 4	<0.025	75 ± 3	ns
P_3	107 ± 6	ns	108 ± 3	ns	90 ± 4	<0.025	90 ± 3	<0.025
N_3	—	—	—	—	112 ± 5	ns	117 ± 3	<0.01

Abbreviations: PTN, posterior tibial nerve; ns, not significant.

[a] Absolute (mean ± SEM) values during blockade are not present because SEPs were abolished in 0, 1, 4, and 2 patients during stimulation of PTN, S-1, L-1, and T-10, respectively.

[b] Mean ± SEM.

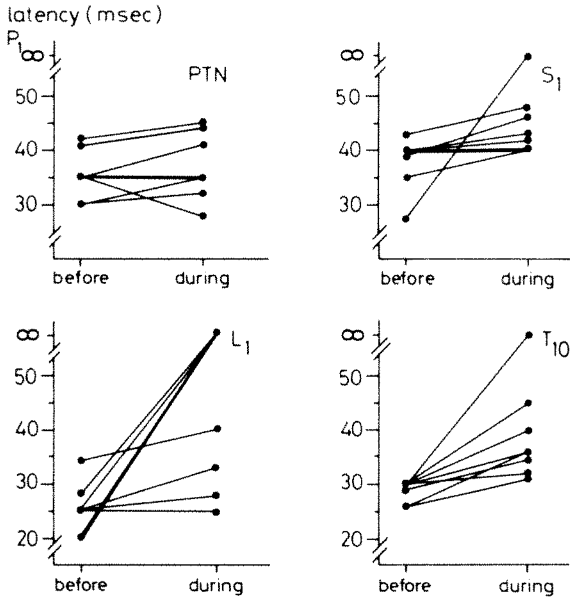

Figure 2. Latency of the first positive peak (P_1) after stimulation at four sites (see text) before and during epidural blockade with bupivacaine, 0.5%. The increase is statistically significant ($P < 0.05$) after stimulation at three dermatomal levels (T-10, L-1, S-1), but insignificant at the posterior tibial nerve ($n = 8$).

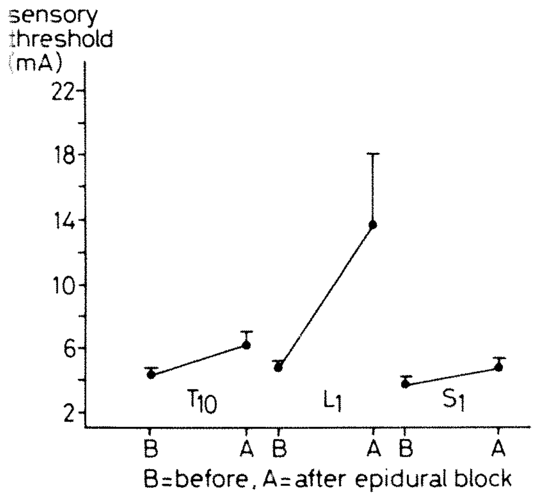

Figure 3. Sensory thresholds before and during epidural blockade with bupivacaine, 0.5% (values are mean ± SEM, $n = 8$). The increase was statistically significant ($P < 0.05$) at T-10 and L-1 but not at S-1.

In studies using electrical dental pulp stimulation, direct infiltration with local anesthetics abolished the cortical evoked response (6,16). SEP after radial nerve stimulation also disappeared completely after pressure and conduction block (21). No studies are available on the effect of spinal anesthesia on SEP.

The relative contribution of various nociceptive fibers to the SEP components has been studied and discussed in detail (22), but no final picture has emerged. However, stimuli passing through Aδ-fibers most likely contribute to the early components of the SEP, whereas other stimuli passing through C-fibers probably may evoke potentials presenting latencies above 500 msec (22).

In conclusion, our study has shown that lumbar epidural analgesia with plain bupivacaine 0.5% may decrease amplitude and increase latency of some of the early components of cortical SEP after electrical stimulation of sensory and mixed motor sensory nerves. The most pronounced changes were seen at the level where the concentration of the local anesthetic agent presumably is highest. However, during clinically effective epidural anesthesia, as assessed by pinprick, afferent neural stimuli apparently pass through an expected blocked area. These findings, if extended, may be of importance when assessing pain syndromes with diagnostic blocks. We think SEP may be of value in future clinical evaluations of neural blockade and possible differential effects of various local anesthetics, as well as of other inhibitors of nociceptive transmission when administered epidurally or intrathecally.

This study was supported by a grant from ASTRA, AB, Södertalje, Sweden, and the Neuromatic 2000 neuromyograph was kindly placed at our disposal by DANTEC/DISA, Copenhagen, Denmark.

References

1. Rocco AG, Raymond SA, Murray E, Dhingra U, Freiberger D. Differential spread of blockade of touch, cold, and pinprick during spinal anesthesia. Anesth Analg 1985;64:917–23.
2. Cusick JF, Myklebust JB, Abram SE. Differential neural effects of epidural anesthetics. Anesthesiology 1980;53:299–306.
3. Rosenberg PH, Heinonen E. Differential sensitivity of A and C nerve fibres to long-acting amide local anaesthetics. Br J Anaesth 1983;55:163–7.
4. Bromm B. The measurement of pain in man. In: Pain measurement in man. Neurophysiological correlates of pain. New York: Elsevier, 1984;3–13.
5. Carmon A, Dotan Y, Sarne Y. Correlation of subjective pain experience with cerebral evoked response to noxious thermal stimulation. Exp Brain Res 1978;33:445–53.
6. Chatrian GE, Canfield RC, Knauss TA, Lettich E. Cerebral responses to electrical tooth pulp stimulation in man. An objective correlate of acute experimental pain. Neurology 1975;25:745–57.
7. Chudler EH, Dong WK. The assessment of pain by cerebral evoked potentials. Pain 1983;16:221–44.
8. Chapman CR, Chen ACN, Harkins SW. Brain evoked potentials as correlates of laboratory pain: a review and perspective. In: Bonica JJ, Liebeskind JC, Albe-Fessard D, eds. Advances in pain research and therapy, vol. 3. New York: Raven Press, 1979:791–803.
9. Carmon A, Friedman Y, Coger R, Kenton B. Single trial analysis of evoked potentials to noxious thermal stimulation in man. Pain 1980;8:21–32.
10. Bromm B, Scharein E. Principal component analysis of pain-related cerebral potentials to mechanical and electrical stimulation in man. Electroencephalogr Clin Neurophysiol 1982;53:94–103.
11. Chapman CR, Colpitts YM, Benedetti C, Butler S. Event-related potential correlates of analgesia: comparison of fentanyl, acupuncture and nitrous oxide. Pain 1982;14:327–37.
12. Sebel PS, Flynn PJ, Ingram DA. Effect of nitrous oxide on visual, auditory and somatosensory evoked potentials. Br J Anaesth 1984;56:1403–7.
13. Sebel PS, Ingram DA, Flynn PJ, Rutherford CG, Rogers H. Evoked potentials during isoflurane anaesthesia. Br J Anaesth 1985;57:340.
14. Pathak KS, Brown RH, Cascorbi HF, Nash CL. Effects of fentanyl and morphine on intraoperative somatosensory cortical-evoked potentials. Anesth Analg 1984;63:833–7.
15. Grundy BL, Brown RH, Greenberg PS. Diazepam alters cortical evoked potentials. Anesthesiology 1979;51:538.
16. Gehrig JD, Colpitts YH, Chapman CR. Effects of local anesthetic infiltration on brain potentials evoked by painful dental stimulation. Anesth Analg 1981;60:779–82.
17. Saugbjerg P, Asoh T, Lund C, Kühl V, Kehlet H. Effects of epidural analgesia on scalp recorded somatosensory evoked potentials to posterior tibial nerve stimulation. Acta Anaesthesiol Scand 1986;30:400–3.
18. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesthesiol Scand 1975;16:55–61.
19. Galindo A, Hernandez J, Benavides O, Ortegon de Munoz, Bonica JJ. Quality of spinal extradural anaesthesia: the influence of spinal nerve root diameter. Br J Anaesth 1975;47:41–7.
20. Kehlet H. The stress response to anaesthesia and surgery: release mechanisms and modifying factors. Clin Anaesthesiol 1984;2:315–39.
21. Bromm B, Neitzel H, Tecklenburg A, Treede R-D. Evoked cerebral potential correlates of C-fibre activity in man. Neurosci Lett 1983;43:109–14.
22. Bromm B. Pain related components in the cerebral potential. Experimental and multivariate statistical approaches. In: Bromm B, ed. Pain measurement in man. Neurophysiological correlates of pain. Amsterdam: Elsevier 1984:257–90.

ANESTH ANALG
1987;66:39–46

Absence of β-Adrenergic Receptor Involvement in Cerebrovascular Dilation by Halothane in Monkeys

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NIKKI PH, NEMOTO EM, BLEYAERT AL, TAYLOR FH, WINTER PM. Absence of β-adrenergic receptor involvement in cerebrovascular dilation by halothane in monkeys. Anesth Analg 1987;66:39–46.

We determined, in monkeys, whether halothane-induced cerebrovascular dilation is mediated by β-adrenergic receptors and whether cerebrovascular tone progressively returns to baseline values during prolonged halothane anesthesia. Total cerebral blood flow (CBF), cerebral perfusion pressure, plasma halothane concentration, and arterial blood gas tensions and pH were measured in 14 rhesus monkeys mechanically ventilated with 0.5% (inspired) halothane, 33% O_2 and balance N_2O. Halothane was increased to 2.0% and the measurements repeated 30 and 60 min later. Then either 0.9% NaCl (controls $n = 6$) or propranolol ($n = 8$), 1.0 mg/kg was infused intravenously over 10 min, and the measurements repeated at 70, 90, 120, and 150 min. After 30 min at 2.0% halothane, CBF increased in the controls by 50% ($P < 0.05$) from 92 ± 8 ($\bar{X}$ ± SD) to 137 ± 39 ml·100 g^{-1}·min^{-1} and in the propranolol group by 30% ($P < 0.05$) from 106 ± 33 to 137 ± 28 ml·100 g^{-1}·min^{-1}. After 2.5 hr of 2.0% halothane anesthesia, CBF remained elevated above baseline levels, but by only 28 and 23% in the control and propranolol groups, respectively. Cerebrovascular resistance was identical in both groups (0.55 ± 0.33 vs 0.53 ± 0.13 mm Hg·ml^{-1}·100 g^{-1}·min^{-1}). The results show that there is only a 10–20% return of CBF toward baseline levels after up to 2.5 hr of 2% halothane anesthesia. The results also indicate that halothane-induced cerebrovascular dilation is not mediated by β-adrenergic receptors.

Key Words: ANESTHETICS, VOLATILE—halothane. BRAIN—blood flow.

Halothane increases cerebral blood flow (CBF) in a concentration-dependent manner in humans (1,2) and animals (3,4); maximal cerebrovascular dilation and complete loss of autoregulation occurs at inspired concentrations of about 2% (3). Albrecht et al. (5) reported an initial 208% increase in CBF with 1% inspired halothane in the goat, which returned to normal within 2.5 hr. In contrast, Warner et al. (6) reported a slower, more gradual restoration of CBF to normal in dogs at 1% halothane (end-tidal concentration). Cerebral blood flow decreased by 50% from 150 ml·100 g^{-1}·min^{-1} at 2 hr after induction to 75 ml·100 g^{-1}·min^{-1} at 7 hr. The results obtained by Boarini et al. (7) indicate that this restoration of CBF toward normal is not dose-dependent, at least between 0.5 and 1.3% halothane. Thus although both groups of investigators reported that CBF returned to baseline values during prolonged halothane anesthesia, the time course differed markedly. This recovery of halothane-induced cerebrovascular dilation seems to parallel the time-dependent recovery of the cardiovascular and metabolic effects of halothane, both of which involve β-adrenergic receptors (8).

Halothane reportedly directly stimulates β-receptors in the heart, bronchial smooth muscle, and uterus (9). Cerebral blood vessels are well-endowed with β-adrenergic receptors (10,11) whose manipulation directly influences CBF (12,13). The cerebrovascular effects of halothane may also be mediated by β-adrenergic receptors and, thus, like its cardiovascular effects, may recover to baseline levels during prolonged halothane anesthesia. However, in a previous study of the dose-related effects of halothane on CBF autoregulation in monkeys (3), we observed no such changes. Thus the aims of this study were to determine in monkeys the extent to which CBF returns toward baseline values during 2.0% halothane

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This work was supported in part by the Health Research Services Foundation, Pittsburgh, PA, Grant No. U-45.

Received from the Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, and the Department of Anaesthesiology, University Central Hospital of Helsinki, Helsinki, Finland. Accepted for publication July 8, 1986.

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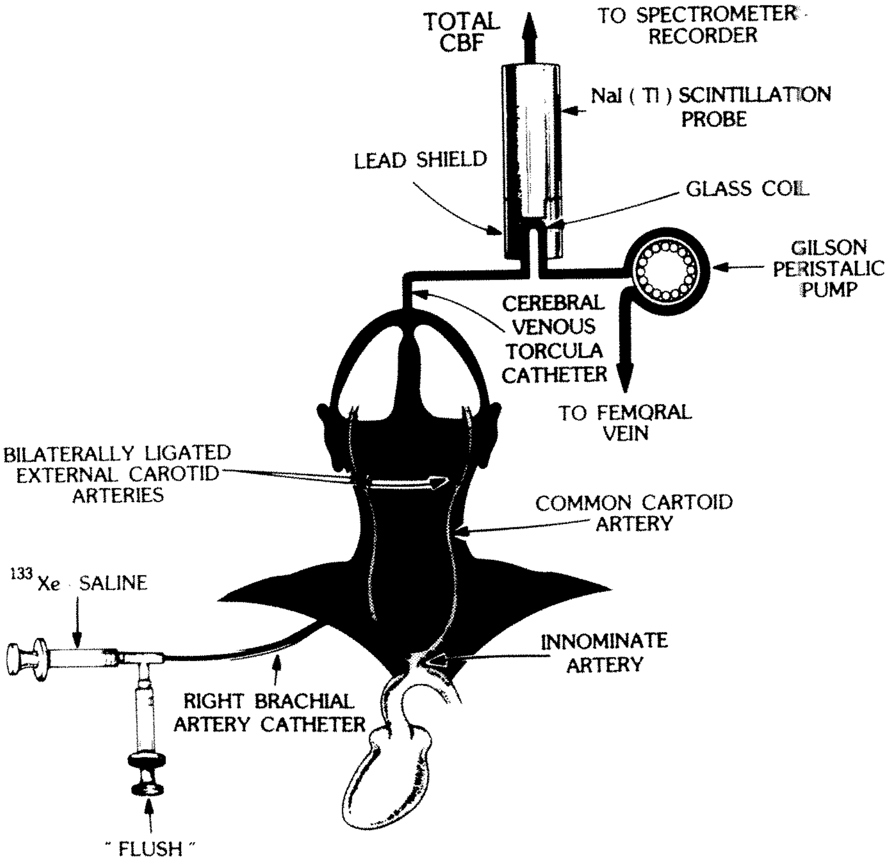
TOTAL CBF
TO SPECTROMETER - RECORDER
NaI (Tl) SCINTILLATION PROBE
LEAD SHIELD
GLASS COIL
GILSON PERISTALIC PUMP
CEREBRAL VENOUS TORCULA CATHETER
TO FEMORAL VEIN
BILATERALLY LIGATED EXTERNAL CAROTID ARTERIES
COMMON CARTOID ARTERY
133 Xe · SALINE
INNOMINATE ARTERY
RIGHT BRACHIAL ARTERY CATHETER
" FLUSH "

Figure 1. System for measurement of total CBF in the monkey. Right brachial artery catheter for ^{133}Xe-saline (500 μCi in 0.2 ml) injection with the catheter tip in the innominate artery for bilateral carotid delivery of the isotope. A "flush" volume of 0.2 ml was used. Both external carotid arteries were ligated to reduce extracranial contamination of rCBF measurements. Cerebral venous blood from the torcula was continuously sampled at about 7 ml/min, passed through a glass coil on the face of a shielded scintillation probe, and returned to the monkey via the femoral vein. Brain ^{133}Xe activity was monitored for at least 10 min after isotope injection.

anesthesia of up to 2.5 hr duration and whether halothane-induced cerebrovascular dilation is mediated by β-adrenergic receptors.

Methods

Fourteen female rhesus monkeys (*Macaca mulatta*, Primate Imports, Inc., New York, NY) weighing 4.0–5.0 kg were quarantined and maintained under the care of a veterinarian. They were fasted overnight with free access to water.

The monkeys were anesthetized with 4% inspired halothane (Fluothane, Ayerst Laboratories, Inc.) in 48% N_2O/48% O_2, intubated with cuffed endotracheal tubes (Portex, 4.0–5.0 mm i.d.), and mechanically ventilated (Model 607 respirator, Harvard Apparatus, Inc.) with 0.5% inspired halothane in 33% O_2, balance N_2O. They were paralyzed with pancuronium bromide (Pavulon, Organon, Inc.), 0.06 mg·kg^{-1}·hr^{-1}, via a catheter inserted percutaneously into the cephalic vein. Tidal volumes were set at 12–15 ml/kg body weight, respiratory rate at 20 breaths/min, and positive end-expiratory pressure (PEEP) at 2–5 cm H_2O. End-tidal CO_2 was continuously monitored (Beckman LB-2 infrared analyzer) and controlled at 5–6% by manipulation of inspired CO_2. Five percent dextrose in 0.45% NaCl containing 100 mEq/L $NaHCO_3$ (to correct for the acidosis that develops during prolonged deep halothane anesthesia) was intravenously infused at 5 ml·kg^{-1}·hr^{-1}; bipolar electrocardiogram was monitored on a polygraph (Model MP-7, Grass Instruments Inc.). Rectal temperature was controlled at 37–38°C with a heated water blanket (Gorman–Rupp Industries) and continuously monitored via a thermistor and telethermometer (Yellow Springs, Inc.).

Polyethylene catheters (PE90, Clay Adams, Inc.) were aseptically inserted into both femoral arteries and veins. Femoral artery catheters were used to monitor arterial blood pressure on the Grass polygraph via a strain-gauge transducer and to withdraw arterial blood samples for measurements of blood gas tensions and plasma halothane concentrations. Femoral vein catheters were used for drug infusions and the reinfusion of blood withdrawn from the extracorporeal circuit for CBF measurements (Fig. 1).

Intracranial pressure (ICP), was measured via a polyethylene catheter (PE50) inserted in the subarachnoid space over the parietal cortex and sealed to the dura with cyanoacrylate glue (Kodak 910 cement). Catheter patency was verified by free backflow of CSF and the presence of arterial and respiratory pulsations.

A Longdwell catheter (18-gauge) was inserted into the torcula and sealed to the dura with cyanoacrylate glue for continuous sampling of cerebral venous blood for the extracorporeal circuit (Fig. 1). Heparin, 150 IU was injected into the torcula to prevent clotting in the sinus and the extracorporeal circuit. Craniectomies were sealed with methylmethacrylate cement.

For the injection of ^{133}Xe-equilibrated saline for CBF measurements, a catheter (PE50) was advanced 12–13 cm via the right axillary artery into the innominate artery to position the catheter tip below the origin of the common carotid artery (Fig. 1).

Table 1. Experimental Protocol

Sample number	Time (min)	Halothane concentration[a] (%)	Treatment	
			Controls ($n = 6$)	Propranolol ($n = 8$)
1	0	0.5	—	—
2	30	2.0	—	—
3	60	2.0	—	—
4	70	2.0	0.9% NaCl	Propranolol (1.0 mg·kg^{-1})
5	90	2.0	—	—
6	120	2.0	—	—
7	150	2.0	—	—

[a] Inspired halothane in 33% O_2, balance N_2O

Experimental Protocol

After surgical preparation, ventilation was continued with 0.5% halothane in 33% O_2 and balance N_2O for a 30-min stabilization period (Table 1). During this time, arterial blood gas tensions were verified to be within the following limits: $Pa_{O_2} > 100$ torr; pHa 7.35–7.45; Pa_{CO_2} 30–35 torr; base deficit ± 5 mEq/L; and MAP 100–125 torr.

After the 30-min stabilization period, a second dose of 150 IU heparin was injected into the torcula. The extracorporeal circuit (Fig. 1) was primed with 0.9% NaCl containing 6 IU heparin/ml. Arterial blood samples were obtained for measurement of blood gas tensions (Corning model 165 trielectrode), hematocrit (1.0 ml), and plasma halothane levels (1.0 ml). Plasma halothane was assayed by gas–liquid chromatography (Varian model 3700) with chloroform as an internal standard (14). Thereafter, 500 μCi of ^{133}Xe in 0.2 ml of 0.9% NaCl was injected into the innominate artery for the first CBF measurement. Inspired halothane concentration was then increased to 2.0% and the measurements repeated 30 and 60 min later. At 2.0% halothane, MAP was kept above 60 torr by titrated intravenous infusion of phenylephrine (Neo-synephrine, 1:1000; Winthrop Labs) and by elevation of the monkeys' legs.

Immediately after the 60-min CBF measurement at 2.0% halothane, either propranolol (Inderal, Ayerst Laboratories, Inc.) 1.0 mg/kg ($n = 8$) or 0.9% NaCl (controls $n = 6$) was infused intravenously over 10 min. CBF and other variables were again measured 0, 30, 60, and 90 min after infusion.

Cerebral Blood Flow Measurement

The method of CBF measurement we used has been previously described (15,16) (Fig. 1). Briefly, CBF was measured by continuous monitoring of cerebral venous ^{133}Xe activity after intraarterial (via the brachiocephalic artery) injection of 500 μCi ^{133}Xe in 0.2 ml saline. Cerebral venous blood was continuously withdrawn from the torcula at a rate of 7 ml/min, passed through a glass coil on the face of a NaI scintillation probe, then through a peristaltic pump, and back into the animal via the femoral vein. The scintillation probe was connected to a spectrometer-ratemeter (Nuclear Chicago, Inc.), and the output recorded on a strip chart recorder. Whole-brain CBF was calculated by stochastic analysis (17,18) according to the following formulas:

$$\mathrm{CBF}\ (\mathrm{ml{\cdot}100\ g^{-1}{\cdot}min^{-1}}) = \lambda \frac{\text{peak height}}{\text{peak area}}$$

where λ is the brain/blood xenon partition coefficient weighted for gray and white matter and corrected for hematocrit according to the equation (19):

$$\lambda = \frac{(1.04)\ (0.744)}{C + 0.787\ (1 - C)}$$

$$\text{where } C = \frac{(0.3)\ (\text{hematocrit})}{34}$$

and 1.04 is the Xe brain/blood partition coefficient for 60% gray matter and 40% white matter at a hemoglobin concentration of 17 g/100 ml or a hematocrit of 57%. Average blood values for rhesus monkeys are: hemoglobin, 12.6 g/100 ml; hematocrit, 42%; and mean corpuscular hemoglobin concentration 30 (20).

Mean arterial pressure (MAP) was calculated as the diastolic pressure plus one-third the pulse pressure; cerebral perfusion pressure (CPP), as the MAP minus the ICP; and cerebrovascular resistance (CVR), from the equation CVR = CBF/CPP.

Statistical comparisons between and within groups were done by analysis of variance for repeated measures and tested for significance by the Student–Newman–Keuls test with a maximum acceptable P value of 0.05.

Table 2. Arterial Blood Gases, pH, Base Excess (BE), Hematocrit (Hct), and Mean Arterial Pressure (MAP) in Six Control (C) and Eight Propranolol (PPL)-Treated Monkeys During Halothane Anesthesia^{a}

	0.5% Halothane^{a}	2.0 Halothane^{a}					
Time (min)	0	30	60	70	90	120	150
Drugs (IV)	None	None	None	PPL/NaCl^{d}			
Pa_{O_2} (mm Hg)							
C	165 ± 11	165 ± 15	154 ± 23	160 ± 19	169 ± 24	168 ± 22	165 ± 21
PPL	154 ± 10	159 ± 60	134 ± 7	131 ± 23	130 ± 23	132 ± 29	134 ± 35
Pa_{CO_2} (mm Hg)							
C	30 ± 3	31 ± 5	33 ± 4	33 ± 4	36 ± 8	37 ± 4	37 ± 5
PPL	34 ± 5	33 ± 4	32 ± 3	35 ± 3	33 ± 3	35 ± 2	33 ± 4
pHa							
C	7.46 ± 0.03	7.41 ± 0.04	7.32 ± 0.09	7.33 ± 0.13^{b}	7.34 ± 0.15^{b}	7.28 ± 0.11^{b}	7.26 ± 0.11^{b}
PPL	7.37 ± 0.06	7.34 ± 0.06	7.40 ± 0.07	7.43 ± 0.04	7.39 ± 0.06	7.36 ± 0.04	7.37 ± 0.06^{c}
BE (mEq/L)							
C	−2.7 ± 0.5	−7.4 ± 2.4	−3.2 ± 3.5	−5.9 ± 7.8	−5.8 ± 7.3	−7.9 ± 6.9	−8.3 ± 5.9
PPL	−4.7 ± 4.8	−6.2 ± 3.4	−3.3 ± 2.7	0.7 ± 3.9	−3.6 ± 2.5	−4.5 ± 3.6	−4.7 ± 1.9
Hct (%)							
C	35 ± 7	34 ± 4	32 ± 6	32 ± 5	31 ± 5^{b}	30 ± 6^{b}	30 ± 5^{b}
PPL	38 ± 2	37 ± 3	34 ± 2	34 ± 2	30 ± 4^{b}	29 ± 3^{b}	28 ± 1^{b}
MAP (mm Hg)							
C	89 ± 22	79 ± 21	79 ± 16	72 ± 16	74 ± 16	74 ± 15	68 ± 17
PPL	106 ± 6	96 ± 10	99 ± 12^{b,c}	89 ± 16	91 ± 14	91 ± 11^{b,c}	83 ± 11

Values are mean ± SD.
[a] In 33% O_2, balance N_2O.
[b] Significant difference compared with value at 0.5% halothane.
[c] Significant difference compared with corresponding value in control group.
[d] 1.0 mg/kg PPL or 0.9% NaCl.

Results

Mean Pa_{O_2} was maintained between 130 ± 23 mm Hg ($\bar{X}$ ± SD) and 169 ± 24 mm Hg Pa_{CO_2} between 30 ± 3 and 37 ± 5 mm Hg in both control and propranolol-treated groups; there was no statistically significant difference between or within groups (Table 2). Arterial pH decreased significantly after 1 hr or longer at 2.0% halothane in the control group, but was not changed in the propranolol group. Thus after 150 min at 2.0% halothane, arterial pH was significantly lower in controls compared with the propranolol-treated monkeys. These differences were also reflected in arterial base excess. Hematocrit decreased progressively and equally in both groups, with the first significant decrease occurring after 70 min at 2.0% halothane in the propranolol-treated monkeys and after 90 min in the controls. Mean arterial pressures were generally lower in the control compared with the propranolol-treated monkeys, but MAP values were significantly lower only after 60 and 120 min on 2% halothane. There was no evidence of a recovery of MAP to baseline values for up to 2.5 hr on 2% halothane.

With 0.5% inspired halothane, mean plasma halothane concentration was 3.1 ± 3.3 mg/dl ($\bar{X}$ ± SD) in the controls and 7.5 ± 1.7 mg/dl in the propranolol-treated monkeys (Table 3, Fig. 2). With 2.0% halothane in both groups, plasma halothane levels ranged between 17.8 ± 3.4 mg/dl and 22.1 ± 7.8 mg/dl with no significant difference between or within groups.

Thirty minutes after halothane was increased from 0.5 to 2.0%, CBF increased by 50% in the control and by 30% in the propranolol group, despite an approximately 20% decrease in CPP (Table 3, Fig. 2). Cerebrovascular resistance decreased by 30–40%. These changes in CBF, CPP, and CVR persisted after 60 min at 2.0% halothane.

Intravenous infusion of either propranolol or saline had no effect on cerebrovascular tone for up to 1.5 hr after infusion. The apparent (but not significant) 11% decrease in CBF from 135 ± 40 ml·100 g^{-1}·min^{-1} before propranolol infusion to 120 ± 23 ml·100 g^{-1}·min^{-1} at the end of infusion was correlated with the decrease in CPP from 67 ± 20 to 59 ± 17 mm Hg. Cerebrovascular resistance was and remained at 0.62 mm Hg·ml^{-1}·100 g^{-1}·min^{-1}. From 30 to 90 min after propranolol infusion mean CBF ranged between 137 ±

Table 3. Cerebrovascular Variables in Six Control (C) and Eight Propranolol (PPL)-Treated Monkeys during Halothane Anesthesia[a]

	0.5% Halothane[a]	2.0% Halothane[a]					
Time (min)	0	30	60	70	90	120	150
CBF (ml·100g^{-1}·min^{-1})							
C	92 ± 8	137 ± 39[b]	124 ± 42[b]	134 ± 50[b]	118 ± 28[b]	115 ± 20[b]	118 ± 18[b]
PPL	106 ± 33	137 ± 28[b]	135 ± 40[b]	120 ± 23[b]	137 ± 40[b]	135 ± 44[b]	130 ± 31[b]
CVR (mm Hg·ml^{-1}·100 g^{-1}·min^{-1})							
C	0.82 ± 0.42	0.66 ± 0.34[b]	0.56 ± 0.30[b]	0.51 ± 0.28[b]	0.57 ± 0.31[b]	0.63 ± 0.31[b]	0.55 ± 0.33[b]
PPL	0.92 ± 0.37	0.57 ± 0.18[b]	0.62 ± 0.24[b]	0.62 ± 0.15[b]	0.57 ± 0.18[b]	0.55 ± 0.18[b]	0.53 ± 0.13[b]
CPP (mm Hg)							
C	83 ± 25	67 ± 24[b]	67 ± 20[b]	59 ± 17[b]	61 ± 19[b]	58 ± 16[b]	53 ± 18[b]
PPL	92 ± 4	75 ± 6[b]	79 ± 5[b]	67 ± 19[b]	70 ± 13[b]	68 ± 8[b]	60 ± 7[b]
Blood halothane (mg %)							
C	3.1 ± 3.3	20.5 ± 6.9[b]	21.3 ± 5.6[b]	20.4 ± 5.0[b]	19.5 ± 5.9[b]	17.8 ± 3.4[b]	20.0 ± 7.3[b]
PPL	7.5 ± 1.7	20.8 ± 0.3	22.0 ± 2.5	21.9 ± 1.6	18.9 ± 1.3	19.5 ± 4.3	22.1 ± 7.8

Values are mean ± SD.

[a] In 33% O_2, balance N_2O.

[b] Significant difference compared with value at 0.5% halothane.

40 and 130 ± 31 ml·100 g^{-1}·min^{-1} and CVR between 0.53 ± 0.13 and 0.57 ± 0.18 mm Hg·ml^{-1}·100 g^{-1}·min^{-1}. In the saline-infused controls, CBF, CVR, and CPP did not change significantly. Cerebral blood flow ranged between 115 ± 20 and 134 ± 50 ml·100 g^{-1}·min^{-1}; CVR, between 0.51 ± 0.28 and 0.63 ± 0.31 mm Hg·ml^{-1}·100 g^{-1}·min^{-1}; and CPP, between 70 ± 13 and 53 ± 18 mm Hg.

Discussion

The dose of propranolol was chosen on the basis of four pilot studies. Monkeys were mechanically ventilated with 0.5% halothane in 33% O_2, balance N_2O. Isoproterenol was infused intravenously at a rate of 0.1 μg·kg^{-1}·min^{-1}, propranolol was administered at various doses, and β-receptor blockade was assessed according to the reversal of the response in heart rate and arterial blood pressure. A cumulative dose of 0.05 and 0.1 mg/kg propranolol had no effect; 0.25 mg/kg caused partial blockade, and 0.75 mg/kg produced total β-receptor blockade. Thus we used a dose of 1.0 mg/kg to ensure complete β-blockade. Other studies also suggest that 1.0 mg/kg propranolol produces complete cerebrovascular β-blockade in the monkey. Hobson et al. (21) used a propranolol dose of 0.5 mg/kg based on its reversal of the effects of isoproterenol on arterial blood pressure in the baboon. On the basis of our pilot studies, a dose of 0.5 mg/kg might have been sufficient to produce complete β-blockade, because 0.25 mg/kg caused partial blockade and 0.75 mg/kg caused complete blockade. Hageman and Pruss (22) used 1.0 mg/kg propranolol in the rhesus and pigtail monkeys. In cats, 1.0 mg/kg propranolol decreased CBF by 30% (23), but did not affect arterial pressure, which suggests that a dose of propranolol that has no significant effect on cardiovascular function has a dramatic effect on cerebrovascular tone. Propranolol, 0.5 mg/kg, injected into the aorta of rabbits did not affect CBF but completely abolished the effects of isoproterenol on CBF (12).

Neither CBF nor CVR returned to baseline values during 2.5 hr of 2% halothane anesthesia in the monkey. These findings differ from those of Albrecht et al. (5), who reported that after 30 min of 1% halothane anesthesia in goats, CBF increased to 208% of the baseline value, decreased to 138% after 60 min, and returned to normal by 150 min. Neither our results nor those of Albrecht et al. (5) can be compared with the findings of Warner et al. (6) or Boarini et al. (7) because they monitored the decay in CBF with the first measurement 2 hr after the induction of anesthesia. In our studies, CBF increased when halothane concentration was raised from 0.5% to 2.0%, and did not change significantly thereafter, in either the propranolol-treated or control group. Between 70 and 90 min after halothane was increased to 2%, mean CBF in the control group declined from 150% to 130% of the value at 0.5% halothane, and this 20% decrease ($P < 0.05$) may be construed as a tendency toward a

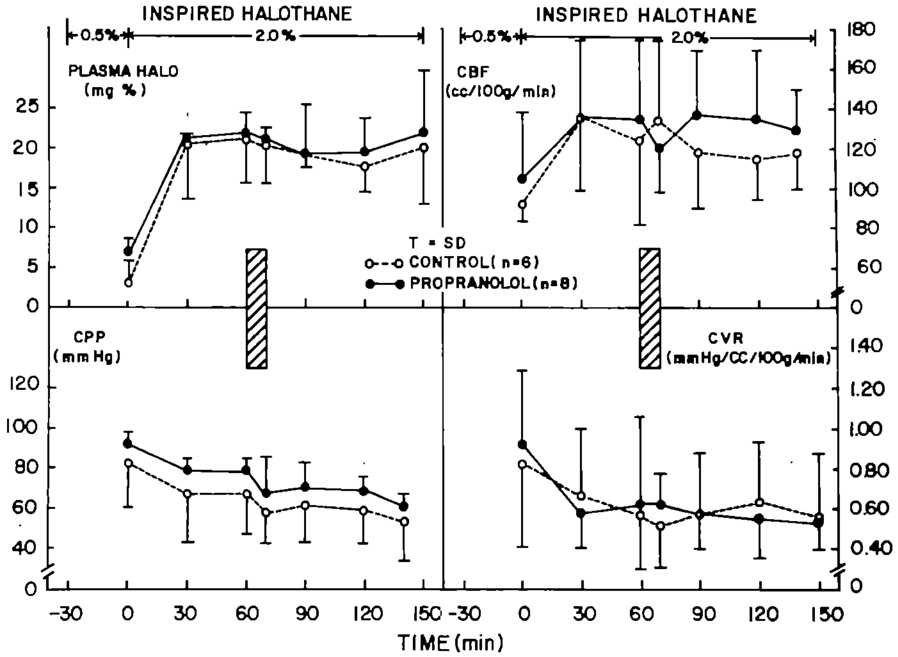

Figure 2. Plasma halothane concentration, cerebral blood flow (CBF), cerebral perfusion pressures (CPP), and cerebrovascular resistance (CVR) in rhesus monkeys during halothane anesthesia. Control monkeys received 3 ml 0.9% NaCl and propranolol-treated monkeys, propranolol 1.0 mg/kg intravenously, between 60 and 70 min (cross-hatched area).

return to baseline. Because CVR did not change, however, this decrease in CBF may be attributed to the decrease in CPP.

Our failure to observe a return of CBF toward baseline values cannot be explained by the decrease in hematocrit or by the tendency of Pa_{CO_2} to increase in the controls. These variables did not change during the first 60 min at 2.0% halothane. Hematocrit decreased significantly after 70 and 90 min in the propranolol and control groups, respectively, but did not change thereafter. Thus the change in hematocrit does not explain the failure of CBF or CVR to return to baseline in the first 60 min at 2.0% halothane or the lack of effect of propranolol on CBF between 70 and 150 min. Furthermore, in the study by Albrecht et al. (5), recovery of CBF was nearly complete after 60 min of halothane. The modest change in mean Pa_{CO_2} in the control group from an initial value of 30 to 33 mm Hg at 70 min and 36 mm Hg at 90 min would be expected to have little effect on CBF because of the buffering capacity of the brain in that range of Pa_{CO_2} (24).

We used phenylephrine during 2.0% halothane anesthesia to avoid severe arterial hypotension, which otherwise would have drastically affected cerebral perfusion pressure and caused hypoxic cerebrovascular dilation. Phenylephrine does not cross the blood–brain barrier or influence CBF (25). If phenylephrine had influenced CBF, one would expect it to have enhanced the return of CBF to baseline, especially in the propranolol-treated monkeys, where its α-adrenergic effects were unopposed by β-adrenergic activity. This was not observed in either the control or the propranolol group.

Recovery of CBF to baseline values during halothane anesthesia in the goat (5) appears consistent with the adaptation of cardiovascular dynamics shown during halothane anesthesia, in man, which was abolished by β-blockade (8). However, cardiovascular dynamics did not return to baseline in the goat (5). If the return of CBF and cardiovascular dynamics to baseline values during halothane anesthesia in the goat occurs by similar mechanisms, then both should be prevented by β-blockade. Albrecht et al. (5) studied the effects of combined α- and β-adrenergic blockade, but the prevention of the return of cardiovascular variables to normal during halothane anesthesia by β-blockade (6) may depend on unopposed α-adrenergic tone. In our study on the monkey, however, neither cardiovascular nor cerebrovascular variables tended to return toward normal during up to 2.5 hr of halothane anesthesia and both were unaffected by β-blockade alone. Thus the lack of cardiovascular recovery provides some support for the lack of cerebrovascular recovery to baseline values. Our failure to observe a recovery of cerebrovascular variables over a 2.5-hr observation period may be because a significant degree of recovery does not occur until 4 hr of halothane anesthesia, as reported by Warner et al. (6). We do not believe that this is a very likely explanation, however, because Albrecht et al. (5) reported recovery of CBF to baseline values within 1.5 hr of halothane anesthesia and, as described later, we believe that the reduction in CBF described by Warner et al. over a 7-hr observation period represents a deterioration of the animal preparation.

Direct measurement of CBF in the goat model has obvious advantages and has been extensively evaluated (26–28), but the role of the goat's prominent carotid rete on CBF and CBF regulation remains undefined. In the goat, the carotid rete is a plexiform vascular arrangement in the posterior pituitary fossa, which, like other areas such as the area postrema, has no blood–brain barrier (29,30). This may explain the exaggerated cerebrovascular response of this model to exogenously administered catecholamines (31), which is a function of blood–brain barrier permeability (32). The marked reduction in CBF caused by electrical stimulation of extrinsic sympathetic nerves (31) could also indicate extensive sympathetic innervation of retial blood vessels. Thus the rapid return of CBF to baseline during 1.5 hr of 1% halothane anesthesia in the goat may result from increased permeability and sensitivity in the carotid rete.

The difference between our results and those of Albrecht et al. (5) may also be due to our higher inspired halothane concentration—2.0% compared with 1.0%—which could have caused different levels of circulating catecholamines. Despite earlier reports that halothane anesthesia either did not change or decreased plasma norepinephrine levels (33–35), light surgical halothane anesthesia increases the plasma catecholamine level by 30%, and deep halothane anesthesia suppresses it by 50% (34). Recently, Joyce et al. (36) reported that in humans plasma norepinephrine levels increase by about 150% after 10–12 min at an end-tidal halothane concentration of 1.5%. Thus the variable effect of halothane anesthesia on plasma catecholamines may alter its cerebrovascular effects, depending on whether (to what extent) circulating catecholamines penetrate the blood–brain catecholamines penetrate the blood–brain barrier.

Warner et al. (6) and Boarini et al. (7) reported a return of CBF toward baseline values over 7 hr of 1% halothane anesthesia. However, the parallel decrease in $CMRO_2$ indicates a general physiologic deterioration of the animal preparation similar to that observed during prolonged barbiturate anesthesia in the dog (37). Their data contrast with the rapid return of CBF to baseline values within the first 1.5 hr of 1% halothane anesthesia reported by Albrecht et al. (5) in the goat. Furthermore, in the goat, as CBF returned toward baseline over the 150-min observation period, $CMRO_2$ progressively returned toward normal values after the initial depression at the onset of anesthesia, unlike the gradual decrease in $CMRO_2$ reported by Warner et al. (6). Clearly, the return of CBF toward baseline during prolonged halothane anesthesia reported by Warner et al. (6) and Albrecht et al. (5) are different phenomena. The phenomenon as reported in the goat may be unique to the goat model at 1% (inspired) halothane anesthesia and does not occur in the monkey at least at 2.0% inspired halothane. Reports revealing marked differences in the adrenergic mechanisms influencing cerebrovascular tone in different animals and humans (38,39) accentuate the likelihood that at least some of the differences in the results obtained are attributable to differences between species.

Our results suggest that unlike the metabolic effects of halothane on lipolysis in the epididymal fat pads in rats (40) and adipose tissue in humans (41), its cerebrovasodilatory effects are not *primarily* mediated by β-adrenergic receptors. These findings are consistent with the observation that the smooth-muscle–relaxing effects of halothane, which apparently are mediated by cyclic-AMP (41–44), are unaffected by β-receptor blockade (45). Triner et al. (45) showed that halothane directly activates adenylate cyclase, which could lead to cAMP accumulation (42) and, in turn, to cerebrovascular dilation.

Halothane (Fluothane) was generously provided by Ayerst Labs, Inc. The authors gratefully acknowledge the helpful comments of Dr. Robert Willenkin, the editorial assistance of Ms. Lisa Cohn, and the secretarial assistance of Ms. Betty Jacobson.

References

1. Wollman H, Alexander SC, Cohen PJ, Chase PE, Malman E, Mehar MS. Cerebral circulation of man during halothane anesthesia: effect of hypocarbia and *d*-tubocurarine. Anesthesiology 1964;25:180–4.
2. Christensen MS, Hoedt-Rasmussen K, Lassen NA. Cerebral vasodilatation by halothane anaesthesia in man and its potentiation by hypotension and hypercapnia. Br J Anaesth 1967;39:927–34.
3. Morita H, Nemoto EM, Bleyaert AL, Stezoski SW. Brain blood flow autoregulation and metabolism during halothane anesthesia in monkeys. Am J Physiol 1977;233:H670–6.
4. Miletich DJ, Ivankovich AD, Albrecht RF, Reimann CR, Rosenberg R, McKissic ED. Absence of autoregulation of cerebral blood flow during halothane and enflurane anesthesia. Anesth Analg 1976;55:100–9.
5. Albrecht RF, Miletich DJ, Madala LR. Normalization of cerebral blood flow during prolonged halothane anesthesia. Anesthesiology 1983;58:26–31.
6. Warner DS, Boarini DJ, Kassell NF. Cerebrovascular adaptation to prolonged halothane anesthesia is not related to cerebrospinal fluid pH. Anesthesiology 1985;63:243–8.
7. Boarini DJ, Kassell NF, Coester HC, Olin JJ, Sprowell JA, Sokoll MD. Comparison of the systemic and cerebrovascular effects of isoflurane and halothane (Suppl. 1). J Cereb Blood Flow Metab 1983;3:S558–559.
8. Price HL, Skousted P, Pauca AL, Cooperman LH. Evidence of

beta-receptor activation produced by halothane in normal man. Anesthesiology 1970;32:389–95.

9. Kilde AM, Penna M, Aviado DM. Stimulation of adrenergic beta receptors by halothane and its antagonism by two new drugs. Anesth Analg 1969;48:58–65.
10. Sercombe R, Aubineau P, Edvinsson L, Mamo H, Owman CH, Seylaz J. Pharmacological evidence in vitro and in vivo for functional betal receptors in the cerebral circulation. Pflugers Arch 1977;368:241–4.
11. Harik SI, Sharma VK, Wetherbee JR, Warren RH, Banerjee SP. Adrenergic and cholinergic receptors of cerebral microvessels. J Cerebral Blood Flow Metab 1981;1:329–38.
12. Aubineau PF, Seylaz J, Sercombe R, Mamo H. Evidence for regional differences in the effect of beta-adrenergic stimulation on cerebral blood flow. Brain Res 1973;61:153–61.
13. Edvinsson L, Lacombe P, Owman CH, Reynier-Rebuffel AM, Seylaz J. Quantitative changes in regional cerebral blood flow of rats induced by alpha- and beta-adrenergic stimulants. Acta Physiol Scand 1979;107:289–96.
14. Wolfson B, Ciccarelli HE, Siker ES. Gas chromatography using an internal standard for the estimation of ether and halothane levels in blood. Br J Anaesth 1966;38:591–5.
15. Kofke WA, Nemoto EM, Hossmann K-A, Taylor F, Kessler PD, Stezoski SW. Brain blood flow and metabolism after global ischemia and postinsult thiopental therapy in monkeys. Stroke 1979;10:554–60.
16. Nemoto EM, Hossmann K-A, Cooper HR. Postischemic hypermetabolism in cat brain. Stroke 1981;12:666–76.
17. Hoedt-Rassmussen K, Sveninsdottir E, Lassen NA. Regional cerebral blood flow in man determined by intra-arterial injection of radioactive inert gas. Circ Res 1966;18:237–47.
18. Zieler K. Equations for measuring blood flow by external monitoring of radioisotopes. Circ Res 1965;16:309–21.
19. Veall N, Mallett HL. The partition of trace amounts of xenon between human blood and brain tissue of 37°C. Phys Med Biol 1965;10:375.
20. Bourne GH. Collected anatomical and physiological data from the rhesus monkey. In: Bourne GH, ed. The rhesus monkey, Vol. 1, Anatomy and physiology. New York: Academic Press, 1975:1–63.
21. Hobson RW, Wright CB, Lamoy RE. Adrenergic mechanisms in the cephalic and cerebral circulations of the subhuman primate. Surgery 1975;77:304–10.
22. Hageman WE, Pruss TP. Cardiovascular profile of 5-methyl-2-phenyl-4-imidazole-acctontrile (MCN-2378), a cerebral vasodilator. Eur J Pharmacol 1975;30:100–6.
23. Davis DH, Sundt TM. Relationship of cerebral blood flow to cardiac output, mean arterial pressure, blood volume, and alpha- and beta-blockade in cats. J Neurosurg 1980;52:745–54.
24. Wasserman AJ, Patterson JL. The cerebral vascular response to reduction in arterial carbon dioxide tension. J Clin Invest 1961;40:1297–303.
25. Smith AL, Neigh JL, Hoffman JC, Wollman H. Effects of general anesthesia on autoregulation of cerebral blood flow in man. J Appl Physiol 1970;29:665–9.
26. Reimann C, Lluch S, Glick G. Development and evaluation of an experimental model for the study of the cerebral circulation in the unanesthetized goat. Stroke 1972;3:322–8.
27. Miletich DJ, Ivankovic AD, Albrecht RF, Toyooka ET. Cerebral hemodynamics following internal maxillary artery ligation in the goat. J Appl Physiol 1975;38:942–5.
28. Anderson B, Jewell PA. The distribution of carotid and vertebral blood in the brain and spinal cord of the goat. Q J Exp Physiol 1956;41:462–74.
29. Schulemann W. Beitrage zur Vitalfarbung. Arch mikr Anat 1912;79:223–46.
30. Bakay L. Studies on blood–brain barrier with radioactive phosphorous. II. Hypophysis and hypothalamus in man. Arch Neurol Psychiat 1952;68:629–40.
31. Lluch S, Gomez B, Alborch E, Urquilla PR. Adrenergic mechanisms in cerebral circulation of the goat. Am J Physiol 1975;228:985–9.
32. McCalden TA, Eidelman BH, Mendelow AD. Barrier and uptake mechanisms in the cerebrovascular response to noradrenaline. Am J Physiol 1977;233:H458–65.
33. Roizen MF, Moss J, Henry DP, Kopin JJ. Effects of halothane on plasma catecholamines. Anesthesiology 1974;41:432–9.
34. Hamelberg W, Sprouse JH, Mahaffey JE, Richardson JA. Catecholamine levels during light and deep anesthesia. Anesthesiology 1960;21:297–302.
35. Price HL, Linde HW, Jones RE, Black GW, Price ML. Sympatho-adrenal responses to general anesthesia in man and their relation to hemodynamics. Anesthesiology 1959;20:563–75.
36. Joyce JT, Roizen MF, Gerson JI, Grobecker H, Eger EI II, Forbes R. Induction of anesthesia with halothane increases plasma norepinephrine concentrations. Anesthesiology 1982;56:286–90.
37. Nemoto EM, Frankel HM. Cerebral oxygenation and metabolism during progressive hyperthermia. Am J Physiol 1970;219:1784–8.
38. Heistad DD, Marcus ML, Gross PM. Effects of sympathetic nerves on cerebral vessels in dog, cat, and monkey. Am J Physiol 1978;235:H544–H552.
39. Toda N. Alpha adrenergic receptor subtypes in human, monkey and dog cerebral arteries. J Pharmacol Exp Ther 1093;226:861–8.
40. Makelainen A, Vapaatalo H, Nikki P. Halothane-induced lipolysis *in vitro* in the rat. Acta Anaesthesiol Scand 1973;17:179–183.
41. Bennis J, Smith U. Studies of the dual effects of halothane on the lipolysis of human fat cells. Anesthesiology 1976;45:379–84.
42. MacMurdo SD, Nemoto EM, Nikki P, Frankenberry MJ. Brain cyclic-AMP and possible mechanisms of cerebrovascular dilation by anesthetics in rats. Anesthesiology 1981;55:435–8.
43. Sprague DH, Yang JC, Ngai SH. Effects of isoflurane and halothane on contractility and the cyclic 3′,5′-adenosine monophosphate system in the rat aorta. Anesthesiology 1974;40:162–7.
44. Yang JC, Triner L, Vulliemoz Y, Verosky M, Ngai SH. Effects of halothane on the cyclic 3′,5′ adenosine monophosphate (cyclic-AMP) system in rat. Anesthesiology 1973;38:244–50.
45. Triner L, Vulliemoz Y, Verosky M. The action of halothane on adenylate cyclase. Mol Pharmacol 1977;13:976–96.

Nitrous Oxide Reduces Thiopental-Induced Prolongation of Survival in Hypoxic and Anoxic Mice

John Hartung, PhD, and James E. Cottrell, MD

HARTUNG J, COTTRELL JE. Nitrous oxide reduces thiopental-induced prolongation of survival in hypoxic and anoxic mice. Anesth Analg 1987;66:47–52.

Arnfred's mouse model was used to test the effect of thiopental during hypoxia (5% O_2) and anoxia, with and without simultaneous administration of nitrous oxide. As found by Arnfred and others, thiopental without N_2O more than doubled survival time during hypoxia (from 5.2 ± 0.6 to 13.9 ± 2.6 min). This effect was completely offset by simultaneous use of N_2O (from 13.9 ± 2.6 to 4.8 ± 0.7 min). Thiopental without N_2O also increased survival time during complete anoxia (from 26 ± 1 to 59 ± 1 sec). This effect was diminished by 58% when N_2O was added (from 59 ± 1 to 40 ± 1 sec). We conclude that nitrous oxide diminishes the effect of barbiturates upon survival time in hypoxic and anoxic mice.

Key Words: BRAIN—hypoxia. ANESTHETICS, GASES—nitrous oxide. ANESTHETICS, INTRAVENOUS—thiopental. HYPOXIA—cerebral.

In 1962 Arnfred and Secher subjected mice to hypoxia (5% oxygen) and found that thiopental more than doubled survival time (1). Two years later Wright and Ames found that prophylactic thiopental doubled survival time in cats subjected to total cerebral ischemia (2). In the following year Wilhelm and Arnfred used the mouse model to test seven additional anesthetics, including ether and nitrous oxide (3). Again thiopental more than doubled survival time. The other agents had modest positive effects, ether had no effect, and nitrous oxide (N_2O) slightly decreased survival time. In order to investigate the possibility of an interactive effect between thiopental and N_2O, we subjected thiopental-anesthetized mice to hypoxia or anoxia with or without nitrous oxide.

Materials and Methods

The effect of thiopental (9–10 mg/100 g body weight intraperitoneally) was tested under four experimental conditions: 1) hypoxia without N_2O, 2) hypoxia with N_2O, 3) anoxia without N_2O, and 4) anoxia with N_2O. All tests were performed on adult (>14 weeks) Swiss white male mice weighing 30–50 g. Each mouse was placed in a 0.5-L Erlenmeyer dispensing flask, and appropriate gas mixtures were delivered through the bottom spout and exhausted through a one hole stopper. A hinged flap was calibrated with weights to stand at 45° when flow was 6 L/min. When gas mixtures were changed, flow rates were briefly turned to 15–20 L/min in order to flush the vessel (Fig. 1). All gas mixtures were delivered from premixed certified tanks, except air, which was delivered from a laboratory outlet.

After Arnfred's protocol (1), mouse survival time was measured to the last perceptible breath. Survival times were compared across groups by one-way analysis of variance, and individual comparisons were made by *t*-tests.

Hypoxia

Mice were divided into four groups. Group 1h received thiopental and breathed 21% O_2 balance N_2 for 15 min before being switched to 5% O_2 balance N_2 (actual O_2 = 5.15%, *n* = 30). Group 2h served as control for group 1, receiving the same treatment without thiopental (*n* = 20). Group 3h received thiopental and breathed 21% O_2, 50% N_2O balance N_2 for 15 min before being switched to 5% O_2, 50% N_2O balance N_2 (actual O_2 = 5.21%, *n* = 30). Group 4h served as control for group 3h, receiving the same treatment without thiopental (*n* = 20).

Individual mice were chosen at random and were

This paper was presented in part at the 1985 Meeting of the American Society of Anesthesiologists, San Francisco, CA. Anesthesiology 63:3A:A413.

Received from the Department of Anesthesiology, State University of New York Health Sciences Center at Brooklyn, Brooklyn, New York. Accepted for publication August 20, 1986.

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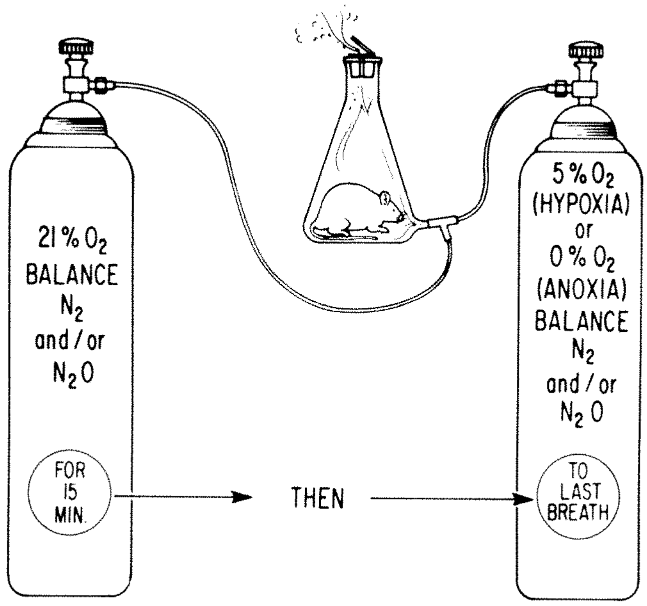

Figure 1. Time to last breath during hypoxia or anoxia was tested with and without thiopental, each with and without simultaneous N_2O. See methods for eight separate experimental treatments, and Figures 2 and 3 for results.

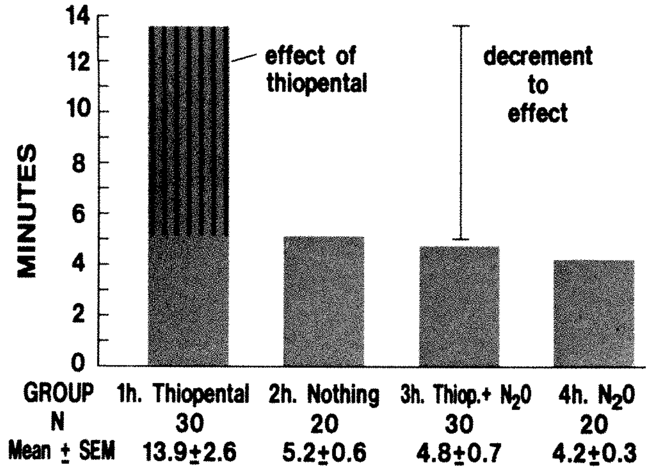

Figure 2. Hypoxia survival time (group 2h) was more than doubled by thiopental (group 1h). Simultaneous use of N_2O (group 3h) diminished that effect by 105% (group 1h − group 3h ÷ group 1h − group 2h). All comparisons to group 1h are significant, other comparisons are not significant ($P \leq 0.01$, ANOVA and t-tests).

tested consecutively across groups (one for group 1h, then one for group 2h, then one for group 3h, etc.) in order to distribute artifacts across groups as evenly as possible (e.g., fluctuations in ambient temperature, time of day, etc.).

Anoxia

The above protocol was repeated, except that all mice were switched to an anoxic rather than a hypoxic mixture. Group 1a received thiopental and breathed 21% O_2 balance N_2 for 15 min before being switched to 100% N_2 ($n = 30$). Group 2a served as control for group 1a, receiving the same treatment without thiopental ($n = 20$). Group 3a received thiopental and breathed 21% O_2 balance N_2O for 15 min before being switched to 30% N_2 balance N_2O ($n = 30$). Group 4a served as control for group 3a, receiving the same respective treatment without thiopental ($n = 20$).

Technical Notes

Male mice have large and fully retractable testicles, with the internal scrotum covering nearly two-thirds of the abdomen. It is easy to mistake an intrascrotal injection for an intraperitoneal injection. If this happens, or if the injection is subcutaneous, the mouse will not become fully anesthetized and will continue to be startled by the rap of a pencil on the side of the flask. The opposite difficulty also exists—an adult male mouse's entire peritoneal cavity is not much larger than the bulk of his testicles. Even when using a tuberculin syringe, it is easy to hit a vital internal organ, especially the liver. When this happens, the mouse will die before the end of the stipulated 15-min period that precedes the insult (hypoxia or anoxia).

A 1% solution of thiopental is especially convenient because it allows each animal's weight in grams to represent the portion of 1 ml required (e.g., a 37-g mouse receives 0.37 ml of solution). However, a 1% solution of commercially prepared thiopental would be significantly hypotonic if diluted with the distilled water that comes with pharmaceutical kits. Allowing for the buffer in commercial preparations (5% by weight), we diluted the powder with a 30:45 mixture of H_2O and normal saline.

Results

Thiopental more than doubled survival time during both hypoxia and anoxia, but the central issue here is the effect of simultaneous nitrous oxide.

Hypoxia

Thiopental extended the time to last breath by 167% when not used in conjunction with N_2O (group 1h − group 2h ÷ group 2h; as found previously, this effect varied substantially across individual mice). The simultaneous thiopental/N_2O group (group 3h) addresses the issue of the interactive effect between thiopental and nitrous oxide. During hypoxia, N_2O completely offset the effect of thiopental (Fig. 2).

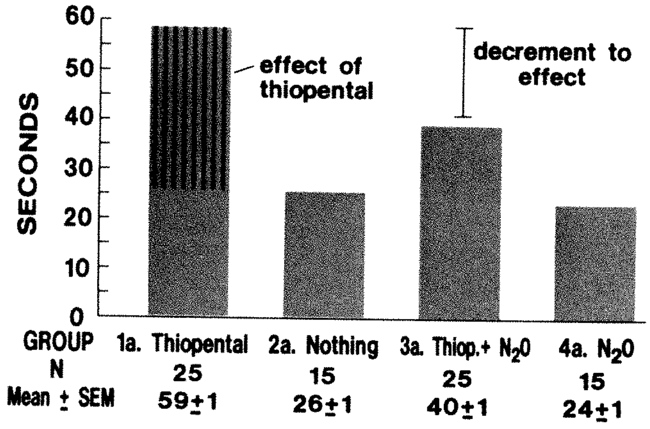

Figure 3. Anoxia survival time (group 2a) was more than doubled by thiopental (group 1a). Simultaneous use of N_2O (group 3a) diminished that effect by 58% (group 1a − group 3a ÷ group 1a − group 2a). All comparisons are significant except group 2a with group 4a ($P \leq 0.01$, ANOVA and t-tests).

Anoxia

Under complete anoxia, mice die in a remarkably short time (≅ 26 sec, group 2a) with even more remarkable consistency (standard errors for all anoxic survival times rounded to 1). Thiopental extended the time to last breath by 127% when not used in conjunction with N_2O (group 1a − group 2a ÷ group 2a). As with hypoxia, the addition of N_2O under complete anoxia (group 3a) substantially diminished the effect of thiopental, but the magnitude of this decrement was cut in half (58 vs 105%, Figs. 2, 3).

Discussion

We found that thiopental extends mouse survival time during both hypoxia and anoxia. This finding replicates work reported more than 20 yr ago (1,3,4). The new finding here is that nitrous oxide offsets thiopental's protective effect during hypoxia, and substantially diminishes that effect during anoxia.

Many investigators have found protective effects of barbiturates to various combinations of hypoxia and anoxia with or without partial or total cerebral ischemia (1–23), but in the last 12 yr several major studies have conspicuously failed to replicate those results (22,24–32). In the discussion section of a major paper (30) reporting a lack of barbiturate protection during cerebral ischemia, it was observed that two previously reported and highly comparable investigations, those of Goldstein et al. (5) and Steen et al. (28), produced contradictory results. The only methodologic difference between the studies was that the investigation that failed to find that thiopental protected against cerebral ischemia used nitrous oxide (28), whereas the investigation that found that thiopental afforded protection did not use nitrous oxide (5). The following opinion was stated: "Although N_2O may not be as indifferent as hitherto believed, it is most unlikely that it should offset a beneficial effect of the barbiturate" (30).

Our results suggest the opposite possibility, i.e., that N_2O may offset a beneficial effect of barbiturates. Unfortunately, unlike the investigations of Goldstein et al. (5) and Steen et al. (28), few of the experimental or clinical protocols that have tested the effect of barbiturates are sufficiently similar to be directly comparable. Nevertheless, crosstabulation of a comprehensive collection of reports reveals a strong negative association between evidence of barbiturate protection and use of nitrous oxide (Table 1).

Critique of the Model

Although N_2O should not be expected to cause myocardial depression at less than 1 atmosphere (33), two eminently possible confounding effects that may have contributed to our finding are N_2O-induced respiratory depression and N_2O potentiation of thiopental beyond its therapeutic range.

Nitrous oxide may cause appreciable ventilatory depression when administered during hypoxia. If our results were caused by such depression, they have no relevance to patients in whom respiration is controlled by ventilators. Eger has hypothesized that an N_2O-induced increase in cerebral blood flow (CBF) could decrease P_{CO_2} in the brain, which would inhibit stimulation of peripheral chemoreceptors and account for reduction of the ventilatory response to hypoxia (34). However, an increase in CBF induced by N_2O is not likely to offset the marked reduction in CBF caused by thiopental. Accordingly, when CBF is reduced by thiopental, N_2O is not likely to elevate CBF to a level that would inhibit stimulation of peripheral chemoreceptors. If N_2O in our hypoxia model did seriously depress ventilation, we would expect the N_2O-only mice (group 4h) to die substantially sooner than control mice (group 2h). This did not happen (Fig. 2). Equally important, in the presence of complete anoxia, ventilatory depression should not be a disadvantage. In other words, if there is no oxygen to be gained by breathing, breathing less should simultaneously conserve energy and elevate P_{CO_2}. In this case the elevation in P_{CO_2} should somewhat compensate for the decrease in CBF caused by thiopental, thereby removing toxic metabolites faster. Accordingly, if respiratory depression played a significant role in the N_2O-induced decrement to thiopental protection during complete anoxia, it may have slightly decreased that decrement.

Table 1. Use of Nitrous Oxide Associates Negatively with Barbiturate Protection ($n = 33$, $\chi^2 = 10$, $P < 0.01$)

	Barbiturate Protection					
	Evident			Not evident		
Use of N_2O	Reference	Investigator(s)	Year	Reference	Investigator(s)	Year
None	1	Arnfred and Secher	1962			
	2	Wright and Ames	1964			
	3	Wilhjelm and Arnfred	1965			
	4	Wilhjelm	1965			
	5	Goldstein et al.	1966			
	6	Secher and Wilhjelm	1968			
	7	Cockburn et al.	1969	24	Snyder et al.	1979
	8	Yatsu et al.	1972	25	Abramson et al.[f]	1983
	9	Hoff et al.	1973	26	Brain	1986
	10	Smith et al.	1974			
	11	Hoff et al.	1975			
	12	Moseley et al.	1975			
	13	Michenfelder et al.	1976			
	14	Steen and Michenfelder	1978			
	15	Tamura et al.	1979			
	16	Chang et al.	1985			
	17	Todd et al.	1985			
	18	Nussmeier and Slogoff	1986			
Curtailed	19	Wells et al.[a]	1963			
	20	Corkill et al.[b]	1976	27	Ward et al.[g]	1985
	21	Bleyaert et al.[c]	1978			
Substantial	22	Michenfelder and Theye[d,e]	1973	22	Michenfelder and Theye[d]	1973
	23	Corkill et al.[e]	1978	28	Steen et al.	1979
				29	Todd et al.	1982
				30	Gisvold et al.	1984
				31	Aldrete and Cubillos	1984
				32	Gisvold et al.[h]	1984

Articles are numbered as in text and references.

[a] N_2O used only after insult.

[b] N_2O used during surgical preparation only.

[c] N_2O discontinued before insult.

[d] This paper reports two separate experiments and is therefore listed twice.

[e] One could interpret the results of this paper as not showing protection, but the authors claim otherwise.

[f] Dr. Jastremski informed us (personal communication) that analysis of finished findings revealed that statistical significance in favor of protection was "almost reached" in the most severely arrested group. Perhaps this paper should be classified as showing protection.

[g] Used N_2O in OR but not in ICU.

[h] This study used hemodilution, hypertension, hypothermia, and dexamethasone in addition to pentobarbital and nitrous oxide. Treated animals woke up sooner, but there was no statistically significant difference between groups on neural deficit score—especially if the treatment group animal that was excluded from the analysis of postinsult deterioration is included.

Our experimental design did not control for the possibility that N_2O potentiated the effectiveness of thiopental to the extent that the same absolute dose given to group 3h and group 3a would constitute an overdose. This possibility can only be evaluated empirically, by incrementally lowering the thiopental dose in groups 3h and 3a. If the offsetting effect attributed to N_2O were to disappear at a lower dose of thiopental, then we have misinterpreted our results.

Interpretation of Results

If our results are correct, they allow the conjecture that N_2O elevated metabolism in vital brain structures sufficiently to offset, or at least interfere with, the reduction of metabolism caused by thiopental. This interpretation, though speculative, is consistent with the finding that N_2O, when used alone, elevates cerebral glucose utilization (35) and the cerebral rate of oxygen consumption ($CMRO_2$) (36–39) while depleting stores of adenosine triphosphate and phosphocreatine (40).

The fact that mice that received N_2O only (groups 4h and 4a) did not die substantially sooner than control (groups 2h and 2a) suggests the following: 1) any increase in metabolism caused by N_2O is not critical when $CMRO_2$ is not depressed, but may be critical when $CMRO_2$ has been reduced by thiopental, and/or

2) simultaneous thiopental and N_2O produce a negative synergism that is more complex than a straightforward opposition of effects on $CMRO_2$. Both of these possibilities are in agreement with the recent finding of Sakabe et al. that "local cerebral glucose utilization in various brain structures is higher during the combined use of nitrous oxide and pentobarbital anesthesia than that measured during pentobarbital anesthesia alone" (41).

If N_2O elevates cerebral metabolism without causing a concomitant increase in CBF during barbiturate anesthesia, as it has been shown to do during midazolam anesthesia (42), the resulting mismatch between CBF and $CMRO_2$ could be critical during O_2 deprivation.

Considering both our experimental findings (Figs. 2, 3) and the result of our literature search (Table 1), we conclude the following: 1) barbiturates significantly prolong survival in mice subjected to hypoxia or anoxia, 2) nitrous oxide substantially diminishes that effect, and 3) contradictory findings in the literature regarding the protective effect of barbiturates may be in part an artifact of N_2O use.

We thank Bartol Matanic, DVM, for assistance and advice and Ms. Ellen L. Jackson for manuscript preparation.

References

1. Arnfred I, Secher O. Anoxia and barbiturates: tolerance to anoxia in mice influenced by barbiturates. Arch Int Pharmacodyn 1962;139:67–74.
2. Wright RL, Ames A. Measurement of maximal permissible cerebral ischemia and a study of its pharmacologic prolongation. J Neurosurg 1964;21:567–73.
3. Wilhjelm BJ, Arnfred I. Protective action of some anaesthetics against anoxia. Acta Pharmacol 1965;22:93–8.
4. Wilhjelm BJ. Further investigations into the protective action of anaesthetics against anoxia in mice. Acta Pharmacol 1965;22:131–4.
5. Goldstein A Jr, Wells BA, Keats AS. Increased tolerance to cerebral anoxia by pentobarbital. Arch Int Pharmacodyn 1966;161(1)138–43.
6. Secher O, Wilhjelm BJ. The protective action of anaesthetics against hypoxia. Can Anaesth Soc J 1968;15:423–40.
7. Cockburn F, Daniel SS, Phil D, et al. The effect of pentobarbital anesthesia on resuscitation and brain damage in fetal rhesus monkeys asphyxiated on delivery. J Pediatr 1969;75:281–91.
8. Yatsu FM, Diamond I, Graziano C, Lindquist P. Experimental brain ischemia: protection from irreversible damage with a rapid-acting barbiturate (Methohexital). Stroke 1972;3:726–32.
9. Hoff J, Smith AL, Nielsen S, Larson P. Effects of barbiturate and halothane anesthesia on focal cerebral infarction in the dog. Neurologic Surg 1973;24:449–51.
10. Smith AL, Hoff JT, Nielsen SL, Larson P. Barbiturate protection in acute focal cerebral ischemia. Stroke 1974;5:1–6.
11. Hoff JT, Smith AL, Hankinson HL, Nielsen SL. Barbiturate protection from cerebral infarction in primates. Stroke 1975;6:28–33.
12. Moseley JI, Laurent JP, Molinari GF. Barbiturate attenuation of the clinical course and pathologic lesions in a primate stroke model. Neurology 1975;25:870–4.
13. Michenfelder JD, Milde JH, Sundt TM Jr. Cerebral protection by barbiturate anesthesia: use after middle cerebral artery occlusion in Java monkeys. Arch Neurol 1976;33:345–50.
14. Steen PA, Michenfelder JD. Cerebral protection with barbiturates: relation to anesthetic effect. Stroke 1978;9:140–2.
15. Tamura A, Asano T, Sano K, Tsumagari T, Nakajima A. Protection from cerebral ischemia by a new imidazole derivative (Y-9179) and pentobarbital: a comparative study in chronic middle cerebral artery occlusion in cats. Stroke 1979;10:126–9.
16. Chang JL, Chang GL, Nemoto EM, Hung TK, Nemmer JP. Barbiturate protection in experimental spinal cord injury. Anesthesiology 1985;63:A400.
17. Todd MM, Hehls DG, Drummond JC, Spetzler RF, Thompson R, Johnson P. A comparison of the protective effects of isoflurane and thiopental in a primate model of temporary focal cerebral ischemia. Anesthesiology 1985;63:A412.
18. Nussmeier NA, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. Anesthesiology 1986;64:165–70.
19. Wells BA, Keats AS, Cooley DA. Increased tolerance to cerebral ischemia produced by general anesthesia during temporary carotid occlusion. Surgery 1963;54:1:216–23.
20. Corkill G, Chikovani OK, McLeish I, McDonald LW, Youmans JR. Timing of pentobarbital administration for brain protection in experimental stroke. Surg Neurol 1976;5:147–9.
21. Bleyaert AL, Nemoto EM, Safar P, et al. Thiopental amelioration of brain damage after global ischemia in monkeys. Anesthesiology 1978;49:390–8.
22. Michenfelder JD, Theye RA. Cerebral protection by thiopental during hypoxia. Anesthesiology 1973;39:510–7.
23. Corkill G, Sivalingam S, Reitan JA, Gilroy BA, Helphrey MG. Dose dependency of the post-insult protective effect of pentobarbital in the canine experimental stroke model. Stroke 1978;9:10–2.
24. Snyder BD, Ramirez-Lassepas M, Sukhum P, Fryd D, Sung JH. Failure of thiopental to modify global anoxic injury. Stroke 1979;10:135–41.
25. Abramson NS, Safar P, Detre K, et al. Results of a randomized clinical trial of brain resuscitation with thiopental. Anesthesiology 1983;59:A101.
26. Brain Resuscitation Clinical Trial I Study Group. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. N Engl J Med 1986;314:397–403.
27. Ward JD, Becker DP, Miller JD, et al. Failure of prophylactic barbiturate coma in the treatment of severe head injury. J Neurosurg 1985;62:383–8.
28. Steen PA, Milde JH, Michenfelder JD. No barbiturate protection in a dog model of complete cerebral ischemia. Ann Neurol 1979;5:343–9.
29. Todd MM, Chadwick HS, Shapiro HM, Dunlop BJ, Marshall LF, Dueck R. The neurologic effects of thiopental therapy following experimental cardiac arrest in cats. Anesthesiology 1982;57:76–86.
30. Gisvold SE, Safar P, Hendrickx HHL, Rao G, Moossy J, Alexander H. Thiopental treatment after global brain ischemia in pigtailed monkeys. Anesthesiology 1984;60:88–96.
31. Aldrete JA, Cubillos P. Phenytoin improves hemodynamic tolerance and survival after severe hypoxia. Anesth Analg 1984;63:1021–4.

32. Gisvold SE, Safar P, Rao G, Moossy J, Kelsey S, Alexander H. Multifaceted therapy after global brain ischemia in monkeys. Stroke 1984;15:803–12.

33. Eisele JH Jr. Cardiovascular effects of nitrous oxide. In: Eger EI II, ed. Nitrous Oxide/N_2O. New York: Elsevier, 1985:125–51.

34. Eger EI. Respiratory effects of nitrous oxide. In: Eger EI II, ed. Nitrous Oxide/N_2O. New York: Elsevier, 1985:109–21.

35. Crosby G, Crane AM, Sokoloff L. A comparison of local rates of glucose utilization in spinal cord and brain in conscious and nitrous oxide or pentobarbital-treated rats. Anesthesiology 1984;61:434–8.

36. Theye RA, Michenfelder JD. The effect of nitrous oxide on canine cerebral metabolism. Anesthesiology 1968;(Nov, Dec):1119–24.

37. Sakabe T, Kuramoto T, Inque S, Takeshita H. Cerebral effects of nitrous oxide in the dog. Anesthesiology 1978;48:195.

38. Oshita S, Ishikawa T, Yokutsu Y, Takeshita H. Cerebral circulatory and metabolic stimulation with nitrous oxide in the dog. Acta Anaesthesiol Scand 1979;23:177–81.

39. Pelligrino DA, Miletich DJ, Hoffman WE, Albrecht RF. Nitrous oxide markedly increases cerebral cortical metabolic rate and blood flow in the goat. Anesthesiology 1984;60:405–12.

40. Keykhah MM, Smith DS, Englebach I, O'Neil JJ, Harp JR. Effects of high-dose fentanyl on cerebral high energy metabolites during hypoxia. Anesthesiology 1984;61:A368.

41. Sakabe T, Tsutsui T, Maekawa T, Ishikawa T, Takeshita H. Local cerebral glucose utilization during nitrous oxide and pentobarbital anesthesia in rats. Anesthesiology 1985;63:262–6.

42. Hoffman WE, Miletich DJ, Albrecht RF. The effects of midazolam on cerebral blood flow and oxygen consumption and its interaction with nitrous oxide. Anesth Analg 1986;65:729–33.

Pharmacokinetics of Alfentanil in Chronic Renal Failure

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CHAUVIN M, LEBRAULT C, LEVRON JC, DUVALDESTIN P. Pharmacokinetics of alfentanil in chronic renal failure. 1987;66:53–6.

The pharmacokinetics of alfentanil were studied during general anesthesia in nine patients with renal failure and in ten patients with normal renal function. All patients received 0.05 mg/kg alfentanil as an intravenous bolus injection. Plasma concentrations were measured at intervals up to 8 hr, using a specific radioimmunoassay technique. Protein binding was measured by equilibrium dialysis. Elimination half-life and plasma clearance were similar in both groups. The volume of distribution at steady state was greater ($P < 0.02$) in patients with renal failure (405 ± 86 ml/kg) than in patients with normal renal function (281 ± 97 ml/kg). Patients with renal failure had a higher ($P < 0.01$) alfentanil plasma free fraction (0.19 ± 0.06) than patients with normal renal function (0.11 ± 0.03). When kinetic parameters were corrected for protein binding, the unbound volume of distribution and the free drug clearance were unchanged in patients with renal failure. These results suggest that the modification of alfentanil free fraction in renal failure does not induce any change in elimination but may influence the distribution of alfentanil.

Key Words: ANALGESICS–alfentanil. ANESTHETICS, INTRAVENOUS—alfentanil. KIDNEY—chronic renal failure. PHARMACOKINETICS—alfentanil.

Decreased drug protein binding is a frequent finding in patients with renal failure (1,2). This change has been reported mainly with acidic compounds (1) such as thiopental, the free fraction of which is markedly increased in renal failure (3). The plasma protein binding of basic drugs is of much greater variability in renal failure (2). In uremic subjects the protein binding of drugs such as quinidine, desmethylimipramine (4), dapsone (5), and propranolol (6) is unchanged, whereas that of morphine (7) and fentanyl (8) is diminished. Reidenberg and Affrime (5) concluded that in uremic subjects, each basic drug of clinical interest requires individual study. In addition, the increased free fraction has been shown to modify distribution and elimination of drugs that are extensively bound to plasma proteins (3). Alfentanil is a weak base that is 92% bound to plasma proteins, particularly to α_1-glycoprotein (9), and it is uncertain whether renal failure might or might not affect the protein binding of alfentanil and its pharmacokinetics. The purpose of this study was to determine the pharmacokinetics and the plasma protein binding of alfentanil in patients with renal failure.

Methods

The study was carried out on nine patients with chronic renal failure, aged 43 ± 13 yr (mean ± SD) and weighing 61 ± 9 kg, and ten patients with normal renal function, aged 45 ± 13 yr and weighing 59 ± 14 kg. Informed consent had been obtained prior to the study, which was approved by the institutional Board of Paris 5 University. Two patients were oliguric and on long-term hemodialysis and seven patients were in the predialysis state with creatinine clearances below 10 ml/min. All patients had normal hepatic function. Normal patients were ASA Class I or II scheduled for minor peripheral surgical procedures. Renal failure patients were scheduled for creation of arteriovenous fistulas. None had significant blood loss. Premedication consisted of 2 mg lorazepam given orally 2 hr before anesthesia. Anesthesia was induced with thiopental, 5–7 mg/kg IV. Vecuronium, 80 μg/kg, was used for tracheal intubation. Anesthesia was maintained with 60% nitrous oxide in oxygen delivered by mechanical ventilation. Ventilation was adjusted in order to maintain end-tidal CO_2 at approximately 5% (Datascope^R 500 CO_2 analyser). Nasopharyngeal temperature was monitored and maintained between 36.0° and 37.0°C by surface warming. Five to ten minutes after induction of anesthesia, alfentanil, 0.05 mg/kg, was given by an IV bolus (10 sec) injection. In some cases, where analgesia was insufficient, fentanyl was administered in repeated doses of 0.1 mg. Venous blood samples (5 ml) were withdrawn into heparinized tubes from a separate line before, then at 5, 10,

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Received from the Department of Anesthesiology, Hôpital Ambroise Paré, Boulogne sur Seine, France. Accepted for publication August 18, 1986.

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Table 1. Effect of Renal Failure on the Pharmacokinetics of Alfentanil

	Normal	Renal failure
V_1(ml/kg)	130 ± 43	126 ± 50
Vd_{ss}(ml/kg)	281 ± 97	405 ± 86^a
Vd_β(ml/kg)	356 ± 167	415 ± 93
CL (ml·kg^{-1}·min^{-1})	3.1 ± 1.6	3.1 ± 1.5
$t_{1/2\beta}$(min)	90 ± 18	107 ± 44

Values are mean ± SD.

Abbreviations: V_1, initial volume of distribution; Vd_{ss}, total apparent volume of distribution at steady state; Vd_β, total apparent volume of distribution measured by the method of the area under the curve; CL, plasma clearance; $t_{1/2\beta}$, elimination half-life.

$^a P < 0.02$, renal failure versus normal renal function.

Table 2. Plasma Protein Concentrations and Unbound Alfentanil Pharmacokinetic Parameters in Renal Failure and Patients With Normal Renal Function

	Normal	Renal failure
Albumin (g/l)	36 ± 2	35 ± 8
α_1-Glycoprotein (g/l)	0.47 ± 0.16	0.67 ± 0.27
FF	0.11 ± 0.03	0.19 ± 0.06^a
Vd_{FF} (ml/kg)	2580 ± 570	2375 ± 910
CL_{FF} (ml·kg^{-1}·min^{-1})	26.3 ± 8.9	18.5 ± 11.1

Values are mean ± SD.

Abbreviations: FF, free fraction plasma alfentanil concentration; Vd_{FF}, unbound volume of distribution; CL_{FF}, unbound clearance.

$^a P < 0.01$, renal failure versus normal renal function.

15, 30, 60, 90, 120, 180, 240, 300, 360, and 480 min after drug administration.

Alfentanil plasma concentration was determined by radioimmunoassay with a sensitivity of 0.1 ng/ml (10). It was verified in our laboratory that the antibody used for alfentanil radioimmunoassay did not cross-react with fentanyl.

The free fraction (unbound fraction) was measured by equilibrium dialysis at alfentanil concentrations of 50 and 500 ng/ml as previously described (11). The concentration of albumin and α_1-glycoprotein was also measured (12) on preoperative serum samples.

The plasma concentration curves derived from data of individual patients were fitted to a biexponential equation, interpreted as a two-compartment open model, using nonlinear least-squares regression analysis. The following pharmacokinetic parameters were derived: distribution half-life ($t_{1/2}\alpha$); elimination half-life ($t_{1/2}\beta$); volume of the central compartment (V_1); total apparent volume of distribution at steady state (Vd_{ss}) (13); and plasma clearance. The total apparent volume of distribution measured by the area method (Vd_β) was also obtained, using the trapezoidal rule. Pharmacokinetic parameters based on free alfentanil were determined. The unbound clearance was determined by dividing the total drug clearance by the free fraction. The volume of distribution at steady state for unbound alfentanil was determined by dividing the Vd_{ss} by the free fraction. Statistical differences between the data obtained from the patients with renal failure and from the control patients were analyzed by the unpaired *t*-test, and linear regression was used to examine the relationship between alfentanil protein binding and plasma protein levels.

Results

Anesthesia lasted 2.1 ± 1.5 hr in control patients and 2.3 ± 1.0 hr in renal failure patients. Fentanyl was administered in seven patients with normal renal function and in six patients with renal failure. The plasma concentration decay curve was biexponential in all patients. Tables 1 and 2 summarize kinetic data in the normal and renal failure subjects. In each, the plasma free fraction was identical with the two concentrations of alfentanil used in measurements of free fraction by equilibrium dialysis. The free fraction was significantly increased ($P < 0.01$) in patients with renal failure. The decreased protein binding had no effect on V_1, Vd_β, plasma clearance, and $t_{1/2}\beta$, which did not differ between the renal failure and normal subjects. Volume of distribution at steady state increased significantly ($P < 0.02$) in the patients with renal failure. Pharmacokinetic parameters based on the free fraction were unchanged in the presence of renal failure. Plasma concentrations of albumin and α_1-glycoprotein were not significantly different between the two groups of patients (Table 2). No linear correlation could be observed between alfentanil free fraction and the plasma concentration of α_1-glycoprotein.

Discussion

The plasma protein binding of alfentanil in normal patients in the present study was similar to that reported by Meuldermans et al. (9), who reported a 92.1% binding. We observed an increase in the free fraction of alfentanil in patients with renal failure. α_1-Glycoprotein has been reported to be the main binding protein for alfentanil (9), as well for a number of other basic drugs, e.g., lidocaine, propranolol, imipramine, methadone, and quinidine (2). However, although the binding of acidic drugs is generally decreased in plasma of patients with renal failure, e.g., phenytoin (14), salicylates, phenylbutazone (15), and thiopental (3), the binding of basic drugs is much more variable. The uremic unbound protein fraction of diazepam, demethyldiazepam, chloramphenicol (2), and morphine (7) is increased in plasma from patients with renal failure whereas the unbound fraction of desmethylimipramine (4), dapsone (5), propranolol (6), and fentanyl (9) was unchanged. The factors affecting drug binding in renal failure include hypoproteinemia, hyperlipoproteinemia, abnormal protein configuration, and drug displacement by accumulated endogenous and exogenous compounds including drug metabolites. In the present study some of the proposed mechanisms such as hypoproteinemia may be excluded because α_1-glycoprotein and albumin were not modified. The effect of dyslipoproteinemia can be ruled out because alfentanil is poorly bound to lipoproteins (9). An alteration in protein configuration is a possible mechanism to explain the decreased capacity of binding to alfentanil. This hypothesis has been suggested as applicable to other drugs. The binding of sulphonamides in uremia may be low in spite of normal concentrations of serum proteins (16). The magnitude of the decrease of plasma binding of phenytoin in uremic patients was found to be greater than predicted by simple dilution of plasma with phosphate buffer (17). The altered albumin configuration observed in uremia by isoelectric focussing (18) further confirms this mechanism. Furthermore, Boobis (16) described qualitative changes in amino acid content of albumin from uremic subjects that caused a decrease in the association constants between phenytoin (18) and sulphadiazine (16) on the one hand and uremic albumin on the other hand. The decreased protein binding capacity observed in patients with renal failure may also be caused by the accumulation of endogenous compounds or drug metabolites. Inhibition in drug protein binding is seen with several drug metabolites such as phenytoin, phenylbutazone, sulphadiazine, salicylic acid, warfarin, and chloramphenicol (19).

The displacement of drugs from their binding proteins may modify their elimination and their distribution into tissues (20) if the unbound fraction of the drug in the plasma is the only one that crosses cell membranes. The increased free fraction of alfentanil was not, in the present study, associated with any change in its plasma clearance. This suggests that alfentanil elimination is not restricted to the free fraction. Alfentanil is almost completely metabolized in the liver (21). The hepatic extraction coefficient of alfentanil estimated from the clearance has an intermediate value between 0.3 (11,22) and 0.6 (23–25). In the present study, the hepatic extraction coefficient of alfentanil was estimated as 0.3 in both normal and renal failure patients. This value was much greater than the free fraction, even in renal failure, and suggests that both free and bound alfentanil can be extracted by the liver (26). In contrast, the free fraction of thiopental exceeds the hepatic extraction coefficient and this increase in the free fraction led to an increase in the clearance of the drug in patients with renal failure (3). The steady state volume of distribution of alfentanil was increased in patients with renal failure, which may be explained by an increase in the free fraction. This suggests that the alfentanil free fraction may influence distribution of the drug. However no change was observed in V_1 and Vd_β. Therefore, in renal failure patients we can expect to find an increase in concentration at the receptor sites and thus an increase in alfentanil clinical response.

Alfentanil kinetics, based on free drug concentrations (unbound volume of distribution and unbound clearance) did not differ in the renal failure group, compared with the normal renal function group. These data indicate that there is no change in either the ability of the liver to metabolize alfentanil or in alfentanil distribution.

In conclusion, although chronic renal failure was associated with a decrease in alfentanil plasma protein binding, it did not change plasma clearance of alfentanil but did increase Vd_{ss} when total drug concentrations were used for calculations. This suggests that the altered protein binding of alfentanil must be carefully considered, particularly in presence of renal failure.

References

1. Sjoholm I, Kober A, Odar-Cederlof I, Borga O. Protein binding of drugs in uremic and normal serum. The role of endogenous binding inhibitors. Biochem Pharmacol 1976;25:1205–13.
2. Piafsky KM. Disease-induced changes in the plasma binding of basic drugs. Clin Pharmacokin 1980;5:246–62.
3. Burch PG, Stanski DR. Decreased protein binding and thiopental kinetics. Clin Pharmacol Ther 1982;32:212–7.
4. Reidenberg MM, Odar-Cederlof I, Bahr C, Borga O, Stoqvist F. Protein binding of diphenylhydantoin and desmethylimipramine in plasma from patients with poor renal function. N Engl J Med 1971;285:264–7.
5. Reidenberg MM, Affrime M. Influence on disease of binding of drugs to plasma proteins. Ann N Y Acad Sci 1973;226:115–26.
6. Bianchetti G, Graziani G, Brancaccio D, Morganti A, Leonetti G, Manfrin M, Sega R, Gomeni R, Ponticelli C, Morselli PL. Pharmacokinetics and effects of propanolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. Clin Pharmacokin 1976;1:373–84.
7. Olsen GD, Benett WM, Porter GA. Morphine and phenytoin binding to plasma proteins in renal and hepatic failure. Clin Pharmacol Ther 1975;17:677–84.
8. Bower S. Plasma protein binding of fentanyl: the effect of hyperlipoproteinaemia and chronic renal failure. J Pharm Pharmacol 1982;34:102–6.
9. Meuldermans WEG, Hurkmans RMA, Heykants JJP. Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood. Arch Int Pharmacodyn Ther 1982;257:4–19.
10. Michiels M, Hendriks R, Heykants J. Radioimmunoassay of the new opiate analgesics alfentanil and sufentanil. Preliminary

pharmacokinetic profile in man. J Pharm Pharmacol 1983;35:86–93.

11. Ferrier C, Marty J, Bouffard Y, Haberer JP, Levron JC, Duvaldestin P. Alfentanil pharmacokinetics in patients with cirrhosis. Anesthesiology 1985;62:480–4.
12. Mancini G, Carbonara AO, Heremans JF. Immunochemical quantitation of antigens by single radial immunodiffusion. Immunochemistry 1965;2:235–54.
13. Benet LZ, Galeazzi RL. Non-compartmental determination of the steady-state volume of distribution. J Pharm Sci 1979;68:1071–4.
14. Odar-Cederlof I, Lunde P, Sjoqvist F. Abnormal pharmacokinetics of phenytoin in a patient with uraemia. Lancet 1970, ii:831–2.
15. Andreassen F. Protein binding of drugs in plasma from patients with acute renal failure. Acta Pharmacol Toxicol 1973;32:417–29.
16. Boobis SW. Alteration of plasma albumin in relation to decreased drug binding in uremia. Clin Pharmacol Ther 1977;22:147–53.
17. Lunde PKM, Rane A, Yaffe SJ, Lunde L, Sjoqvist F. Plasma protein binding of diphenylhydantoin in man. Clin Pharmacol Ther 1970;11:846–55.
18. Shoeman DW, Benjamin DW, Azarnoff DL. The alteration of plasma proteins in uremia as reflected in the ability to bind diphenylhydantoin. Ann NY Acad Sci 1973;226:127–30.
19. Verbeek RK, Branch RA, Wilkinson GR. Drug metabolites in renal failure: pharmacokinetic and clinical implications. Clin Pharmacokin 1981;6:329–45.
20. Ghoneim MM, Pandya HB, Kelley SE, Fisher LJ, Corry RJ. Binding of thiopental to plasma proteins: effects on distribution in the brain and heart. Anesthesiology 1976;45:635–9.
21. Stanski DR, Hug CC Jr. Alfentanil. A kinetically predictable narcotic analgesic. Anesthesiology 1982;57:435–8.
22. Bower S, Hull CJ. Comparative pharmacokinetics of fentanyl and alfentanil. Br J Anaesth 1982;54:871–901.
23. Bovill JG, Sebel PS, Blackburn CL, Heykants J. The pharmacokinetics of alfentanil (R 39209): a new opioid analgesic. Anesthesiology 1982;57:439–43.
24. Camu F, Gepts E, Rucquoi M, Heykants J. Pharmacokinetics of alfentanil in man. Anesth Analg 1982;61:657–61.
25. Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivates. Clin Pharmacokin 1983;8:422–46.
26. Wilkinson GR, Shand DG. A physiological approach to hepatic drug clearance. Clin Pharmacol Ther 1975;18:377–90.

Integrated Electromyographic Measurement of Abdominal Motor Blockade during Bupivacaine Epidural Anesthesia for Lower Abdominal and Pelvic Surgery

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CHAMBERLAIN DP, CRAWFORD RD. Integrated electromyographic measurement of abdominal motor blockade during bupivacaine epidural anesthesia for lower abdominal and pelvic surgery. Anesth Analg 1987;66:57–63.

The onset and regression of abdominal motor blockade was monitored with integrated electromyography in eighteen patients undergoing pelvic or lower abdominal surgery during lumbar epidural anesthesia using 0.75% bupivacaine with 1:200,000 epinephrine. The integrated electromyograph (EMG) was measured at the T-6, T-8, T-10 and T-12 dermatomes during a standardized head-raising test before anesthesia and at fixed time intervals thereafter for a minimum of four hours. Simultaneous measurements were made of abdominal sensory block (analgesia to Allis forceps pinch expressed in dermatomes) and lower limb motor blockade (Bromage scale). Motor block at a given dermatome level was defined as reduction of the integrated EMG amplitude to less than 20% of control. Mean maximum level of sensory block was T-4.2 ± 0.6 (SEM) mean maximum level of motor block was T-8.8 ± 0.5. The mean motor sensory differential varied between 4.5 ± 0.6 and 5.3 ± 0.9 segments over the 4-hr study period. Mean time to maximum abdominal sensory block was 28 ± 3 min, and maximum abdominal motor block was 29 ± 6 min. Mean time to two-segment regression of abdominal motor block was 94 ± 18 min and to two-segment regression of abdominal sensory block, was 150 ± 18 min.

Key Words: ANESTHETIC TECHNIQUES—epidural.

Spinal and epidural anesthesia produce an upper level of sensory block higher than the upper level of motor block (1,2). The difference between the levels is 1.8 segments in tetracaine spinal anesthesia (1), 2.8 segments in lidocaine spinal anesthesia, and 4.6 segments in lidocaine epidural anesthesia (2).

In the present study the upper levels of sensory and motor blockade were examined in 0.75% bupivacaine epidural anesthesia. As in studies with tetracaine and lidocaine spinal anesthesia, and lidocaine epidural anesthesia, electromyography (3) was used to measure the upper level of motor blockade. Selection of integrated surface electromyography (4) in this study enabled prolonged monitoring to take place. Onset and regression of blockade were examined over a minimum of four hours.

Methods

Eighteen ASA status I or II patients undergoing lower abdominal or pelvic surgery under lumbar epidural anesthesia who had given their informed consent were included in this study.

Four pairs of 5 mm diameter silver/silver chloride EEG electrodes were applied to the abdomen at the dermatomes T-6, T-8, T-10 and T-12. At each level one electrode was placed on the left and one on the right belly of the rectus abdominis muscle. The ground electrode (32 mm disc electrode with connecting wire phone tip, Serial 6008-1) was placed over the greater trochanter. Electrical contact between the skin and the electrodes was achieved using EEG jelly, and electrode position was secured using water-proof adhesive tape.

The recording electrodes were connected to a TECA PA63 (TECA Corporation, Pleasantville, NY) EMG preamplifier. This is a D.C.-coupled differential amplifier which, when switched to the 'common mode', has an input impendence greater than 100 MΩ per 30 pF and a signal rejection greater than 8000:1 at 60 c.p.s. The preamplified signal was then fed through a TECA AA6T EMG amplifier with the HF and LF filters (which

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This study was supported in part by a grant from the American Society of Regional Anesthesia. Presented in part at the Annual Meeting of the American Society of Anesthesiology, October, 1981.

Received from the Virginia Mason Hospital, Seattle, Washington. Accepted for publication August 20, 1986.

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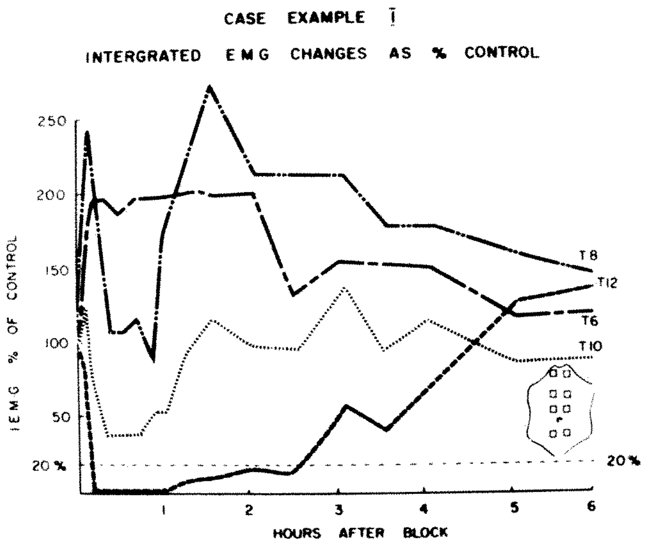
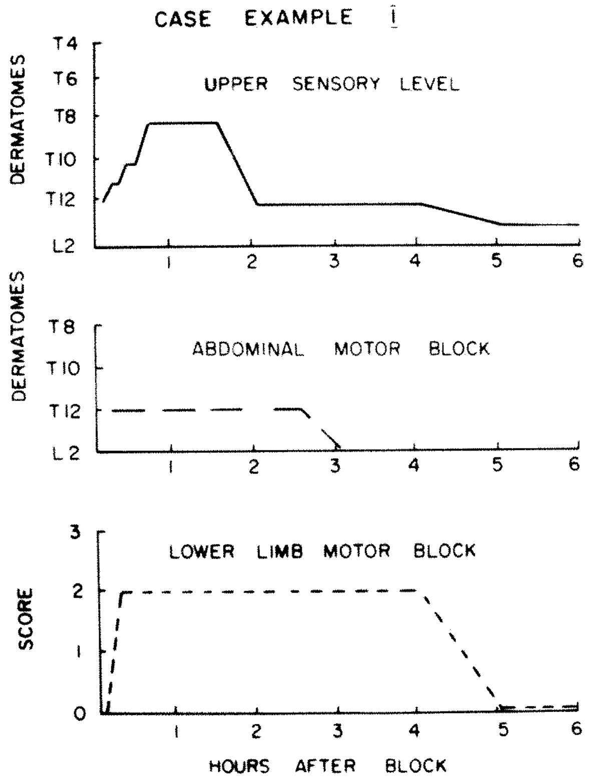


Figure 1. Case 1: Integrated EMG amplitude at T-12, T-10, T-8, and T-6 as a percentage of control.

Figure 2. Case 1: Relationship between abdominal motor block, upper level of sensory block, and degree of lower limb motor block.



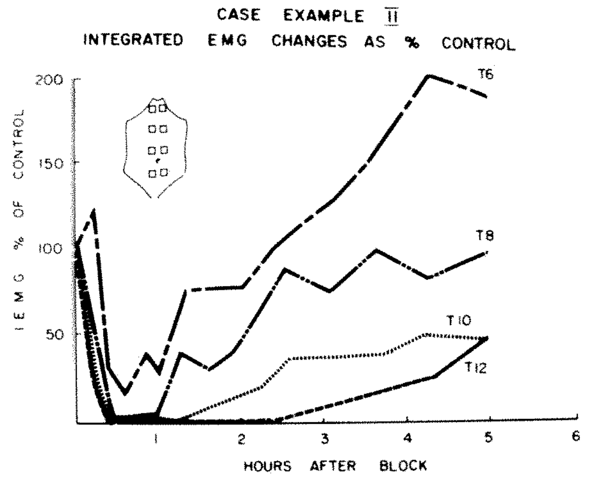
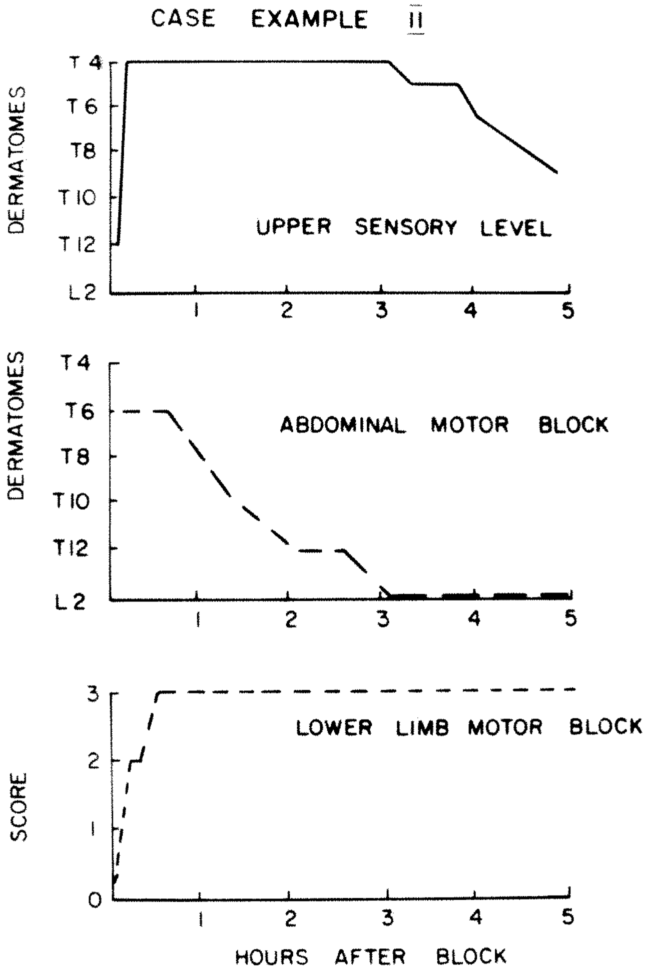


Figure 3. Case 2: Integrated EMG amplitude at T-12, T-10, T-8, and T-6 expressed as a percentage of control after lumbar epidural anesthesia.

Figure 4. Case 2: Relationship between abdominal motor block, upper level of sensory blockade, and lower limb motor blockade.



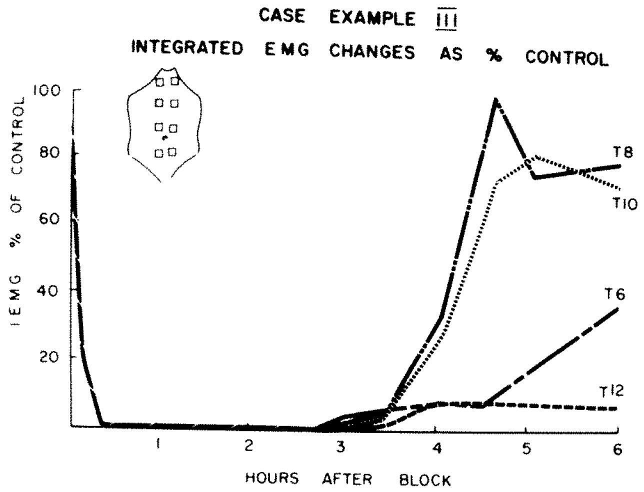


Figure 5. Case 3: Integrated EMG amplitude at T-12, T-10, T-8 and T-6 expressed as a percentage of control after lumbar epidural anesthesia.

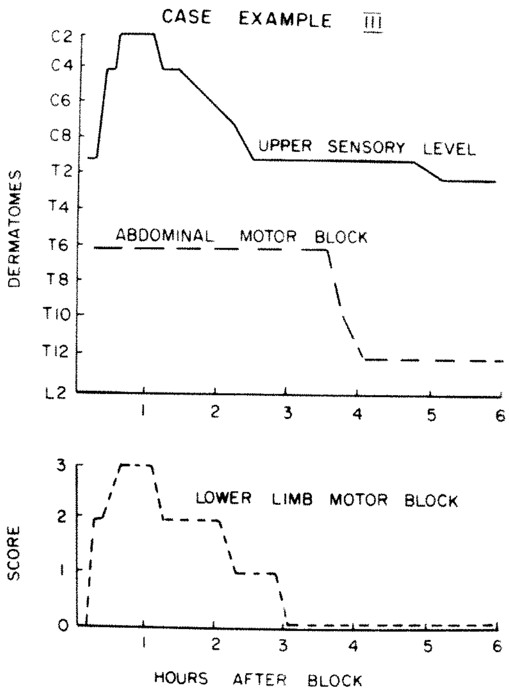


Figure 6. Case 3: Relationship between abdominal motor block, the upper level of sensory blockade, and lower limb motor blockade.

both have an attenuation of 6 dB/octave) to exclude all but the 1,000-10,000 Hz band so that the signal could be monitored without significant interference due to surgical procedures and operating room equipment. The amplified EMG was rectified and integrated by a TECA I6 integrator. In this device the integrator is charged to a pre-set time-constant and the output reflects the mean voltage achieved, when the 'Mean Voltage' mode is used. We found that a time constant of 800 msec gave a smooth deflection during contraction of the abdominal muscles.

Both the raw and integrated EMG were monitored on a Cole-Parmer 2-channel strip-recorder (Model 8373-20). The ECG appeared on the tracings but did not interfere with EMG recordings. Its presence was a useful indicator of the electrical integrity of the circuit (5). A control recording of rectus activity was made at each of the four dermatome levels during a standardized head-raising test. This consisted of the patient raising his head from the supine position until the forehead touched a 2.5 cm diameter ball positioned 20 cm above the patient's nose for a full 5 sec.

Lumbar epidural anesthesia was performed at the L2-3 interspace, with a 19-G spinal needle, by the "loss of resistance" technique, using 20 ml of 0.75% bupivacaine with 1:200,000 epinephrine.

All patients received intravenous infusions of 5% dextrose in lactated Ringer's solution. The patients were monitored with blood pressure cuff, using Korotkoff sounds, ECG and precordial stethoscope. Sedation was maintained at a level compatible with the patient's ability to participate actively in the study with an IV infusion of 0.2% methohexital and/or 50% nitrous oxide in oxygen by mask as required. If deeper sedation or general anesthesia was indicated, this was administered and no further motor or sensory measurements were made.

Following completion of the block procedure, recordings of EMG activity at the four dermatome levels were made every 5 minutes during the head-raising test for 15 min, then every 15 min for 1 hr and thereafter every 30 min until a minimum of 4 hours had elapsed. Simultaneous measurements were made of abdominal sensory block and lower limb motor block. The upper level of abdominal sensory block was taken to be the highest dermatome at which there was analgesia to Allis forceps pinch. Testing was performed bilaterally along the anterior axillary line. If there was a discrepancy between the two sides, the lowermost level was taken as the level of sensory block. Lower limb motor block was measured according to the method of Bromage (6). Again, if a discrepancy existed between the two sides, the lower score was taken as the degree of lower limb motor block.

Abdominal motor block at a given dermatome level was recorded as the level at which the amplitude of the integrated EMG in response to head-raising was reduced to 20% or less of the baseline value. In this manner abdominal motor blockade could be recorded as "T-6 or above", T-8, T-10, T-12, or "below T-12".

The segmental difference, expressed as dermatomes, between upper motor and sensory block levels

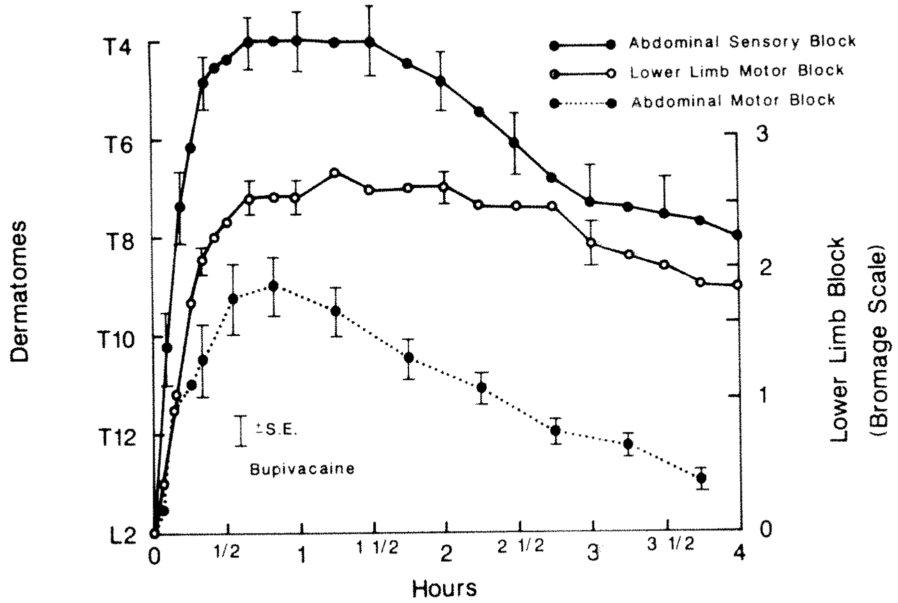


Figure 7. Mean upper level of sensory blockade, mean abdominal blockade, and mean lower limb motor blockade after lumbar epidural anesthesia for the series.

was calculated over the 4-hr period. Differences between the motor and sensory block levels were tested for significance using the Mann–Whitney U-Test.

Linear regression analysis was performed to establish whether, for practical terms, there was a linear relationship between the upper level of sensory blockade and the upper dermatomal level of abdominal motor blockade, or between the upper level of motor blockade and degree of lower limb motor blockade.

This study was approved by the Human Research Committee of the Virginia Mason Research Foundation.

Results

The mean age of the patients was 42.4 ± 10.7 yr (SD), mean weight 64.1 ± 11.8 kg and mean height 159.3 ± 7.4 cm. Two patients were male and 16 were female.

The nature of the data from which our results are drawn is illustrated by three case examples which show poor motor block, moderate abdominal motor block and good abdominal motor block.

Case 1: Poor Abdominal Motor Block

Figure 1 shows the integrated EMG amplitude, expressed as a percentage of control, at the four dermatome levels measured at intervals over a period of 6 hours following lumbar epidural anesthesia in a 43-yr-old patient undergoing vaginal hysterectomy.

Integrated EMG activity at the T-12 level was rapidly abolished following administration of epidural bupivacaine, but began to return after one hour. No block was apparent after 4 hr. At the T-10 level there was an initial increase in activity following epidural injection, but this rapidly declined. Complete motor blockade did not occur and regression of blockade began at 45 min. Transient reduction of the initial increased activity occurred between 10 and 45 min at the T-8 level. At the T-6 level, a marked increase in integrated EMG activity occurred during the period of motor block of the lower segments and this activity returned to control levels as function of the inferior segments recovered.

Figure 2 of this patient shows the relationship between abdominal motor block determined by this technique and the upper level of sensory block and lower limb block. A T-8 dermatomal level of lower abdominal sensory blockade is present from 40 min to 105 min. Complete lower limb block was never achieved but the maximal level occurred from 15 min to 4 hr.

Case 2: Moderate Abdominal Motor Block

Case 2 is a 46-yr-old patient who underwent rectocoele repair. As can be seen in Figure 3 motor block was more intense than in case 1 and complete block occurred at T-12 to T-6 20 minutes after performing the injection. However, despite initial intensity of this block, regression began at 1 hour and was complete by 3 hr.

Figure 4 shows abdominal sensory block, abdominal motor block and lower limb motor block in Case 2. The height of abdominal motor block is seen to have reached T-6 and the duration of blockade at the

Table 1. Time Relationship Between Motor and Sensory Blockade

	Time to nearest minute
Mean time to maximum abdominal sensory block	28 ± 3
Mean time to maximum abdominal motor block	29 ± 6
Mean time to maximum lower limb motor block	30 ± 3
Mean time to two-segment regression to abdominal motor block	94 ± 18
Mean time to two-segment regression of abdominal sensory block	150 ± 18

Values are mean ± SEM.

Table 2. Upper Sensory Block Levels, Abdominal Motor Block Level and Motor–Sensory Differential

	Level expressed as dermatomes
Mean maximum abdominal motor block level	T-8.8 ± 0.5
Mean maximum abdominal sensory block level	T-4.2 ± 0.6
Abdominal motor–sensory differential (15 min–4 hr)	5.2 ± 0.2

Values are mean ± SEM.

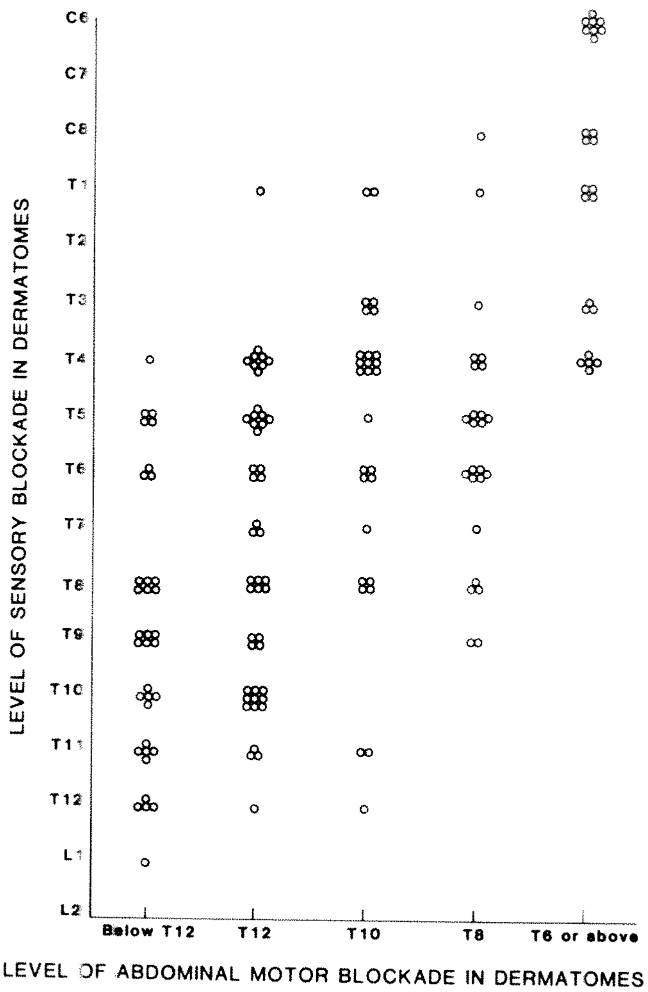


Figure 8. Segmental relationship between the upper level of sensory blockade and abdominal motor blockade.

individual recording levels is shown. Maximum motor block ceased after 45 minutes whereas maximum sensory block persisted from 10 minutes to 3 hours. Complete lower limb block occurred in this case, but was only attained just before maximum motor block started to regress. Complete lower limb block was still present 5 hr after block procedure. This was the pattern of block most commonly encountered.

Case 3: Intense Abdominal Motor Block

In Case 3 a high and very intense block was achieved in a 53-yr-old patient undergoing oophorectomy. Figure 5 shows complete block occurred at all four recording levels within 10 minutes with slow recovery beginning after 2.75 hr. Figure 6 shows the relation of the abdominal motor block pattern to the upper sensory block level and lower limb motor block. It can be seen that the sensory block level was very high and motor block was at T-6 or above for 3.5 hr, levels above T-6 not being recordable by the technique. In this example, lower limb motor block is only complete from 30 min to 1 hr after administering epidural bupivacaine. Thus, in this example, an intense abdominal motor blockade was not accompanied by complete lower limb motor blockade.

The mean levels of abdominal motor block and upper sensory block are shown in Figure 7 together with the mean Bromage scale scores for lower limb motor block. All but four patients developed complete motor block of the legs and regression was much slower than that of abdominal motor block. The time relationship between motor and sensory blockade are shown in Table 1. There was no significant difference in the time taken to develop maximum sensory block (28 ± 3.0 min.) and the time taken to develop maximum abdominal motor block (29 ± 6.0 min.). Nor was there any significant difference in the times to 2 segment regression (94 ± 18 min for abdominal motor block and 150 ± 18 min for abdominal sensory block).

Table 2 shows that mean maximum sensory level achieved was T-4.2 ± 0.6, which was higher than the maximum motor block level of T-8.8 ± 0.5 ($p < 0.002$). The motor-sensory differential varied between 4.5 and 5.5 segments between 30 min and 4 hr. At 4 hr, six

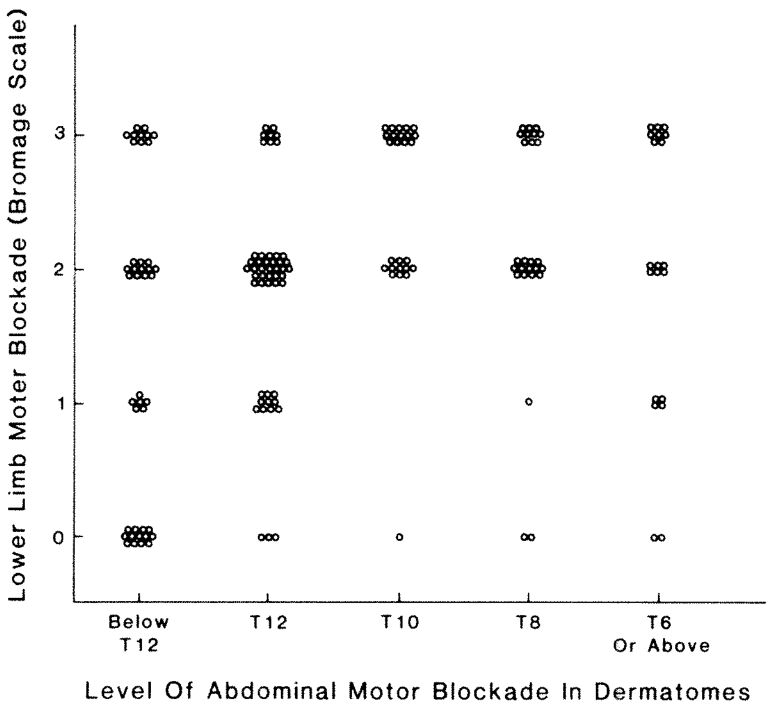


Figure 9. Relationship between lower limb motor blockade and abdominal motor blockade.

patients showed no regression of lower limb motor blockade and only one patient showed complete recovery from lower limb blockade.

Figure 8 and Figure 9 show the segmental relationship between the sensory block level and degree of lower limb motor block with respect to abdominal motor block. All recordings are shown in these figures. Linear regression analysis performed on the data reveals a highly significant relationship between the level of sensory blockade and level of motor blockade ($r = 0.689$). Correlation between lower limb motor blockade and abdominal motor blockade is poorer ($r = 0.25$).

Discussion

We have developed a method of objectively monitoring abdominal motor blockade during surgery under lumbar epidural anesthesia. Fink (3) used the intramuscular electromyograph to monitor abdominal muscular activity during the administration of succinylcholine in patients undergoing general anesthesia. The development of surface integrated electromyography (4) has meant that muscular activity can now be monitored non-invasively.

The method of determining the dermatomal level of abdominal motor blockade which we have described has certain limitations. In order to perform the standardized head-raising test the patient has to be awake and cooperative. In addition, one or more surface electrodes may have to be removed temporarily or permanently if they encroach on the surgical field. If a self-retaining retractor is not used and the head-raising test is performed when abdominal motor blockade is poor or absent, tightening of the abdominal muscles will interfere with surgery. Motor blockade above the T-6 dermatome level or below the T-12 level cannot be assessed by this method.

Using this technique, this study demonstrates that 0.75% bupivacaine with 1:200,000 epinephrine administered via the lumbar epidural route produces a motor-sensory differential of 5.2 ± 0.2 segments. This finding is very similar to the motor-sensory differential of 4.6 segments that Freund et al. found using 15–25 ml of 2% lidocaine with 1:200,000 epinephrine (2). The onset, extent and regression of motor blockade are shown to be more closely related to the onset, extent and regression of sensory blockade than to lower limb motor blockade. We therefore conclude that if the motor-sensory differential for a given local anesthetic solution has been established, the dermatomal extent of sensory blockade provides a more reliable indication of the state of motor blockade than does determination of lower limb motor block.

References

1. Walts LF, Koepke G, Margules R. Determination of sensory and motor levels after spinal anesthesia with tetracaine. Anesthesiology 1964;25:634–7.

2. Freund FG, Bonica JJ, Ward RJ, Akamatsu TJ, Kennedy WF. Ventilatory reserve and level of motor block during high spinal and epidural anesthesia. Anesthesiology 1967;28:834–7.
3. Fink BR. A method of monitoring muscular relaxation by the integrated abdominal electromyogram. Anesthesiology 1960; 21:178–85.
4. Bouisset S, Maton B. Comparison between surface and intramuscular EMG during voluntary movement. In: Desmedt JE, ed. New developments in electromyography and clinical neurophysiology. Vol 1. Basel: Karger, 1973:533–9.
5. Kaul SU, Heath JR, Nunn JF. Factors influencing the development of expiratory muscle activity during anaesthesia. Br J Anaesth 1973;45:1013–8.
6. Bromage PR, Burfoot MF, Crowell DE, Pettigrew RT. Quality of epidural blockade I: influence of physical factors. Br J Anaesth 1964;36:342–52.

ANESTH ANALG
1987;66:64–70

Hemodynamic Effects of Infusions of the Emulsion Formulation of Propofol during Nitrous Oxide Anesthesia in Humans

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COATES DP, MONK CR, PRYS-ROBERTS C, TURTLE M. Hemodynamic effects of infusions of the emulsion formulation of propofol during nitrous oxide anesthesia in humans. Anesth Analg. 1987;66:64–70.

The hemodynamic response to anesthesia with the aqueous emulsion formulation of propofol was studied in healthy patients (ASA I or II), aged 39–57 yr, premedicated with morphine, 0.15 mg/kg. Anesthesia was induced in all patients with propofol, 2 mg/kg. Subsequently, patients were randomly assigned to two groups and maintained by a continuous intravenous infusion (group 1 received 54 $\mu g \cdot kg^{-1} \cdot min^{-1}$, group 2 received 108 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to supplement 67% nitrous oxide. Three minutes after induction, systolic arterial pressure (SAP) decreased 28% ($P < 0.01$) and was associated with decreased (−12%) cardiac output ($\dot{Q}_{70}$) and decreased (−15%) systemic vascular resistance (SVR). The hemodynamic response to tracheal intubation was not obtunded, but peak values of arterial pressures and heart rate did not exceed those recorded awake. Thirty minutes elapsed before repeating measurements prior to the first surgical incision. In group 1, SAP and $\dot{Q}_{70}$ decreased to 65% and 68% of awake values and in group 2 to 55% and 74% ($P < 0.05$). Mild ventilatory depression persisted for the duration of spontaneous ventilation and was not reduced by the stimulus of surgery, which caused no significant hemodynamic responses in either group. Decreasing arterial P_{CO_2} to the awake value by controlled ventilation increased SVR ($P < 0.05$), but the associated increased SAP and decreased $\dot{Q}_{70}$ did not reach statistical significance. No patient reported awareness. The infusion of the emulsion formulation of propofol was associated with satisfactory anesthesia and recovery and with hemodynamic effects similar to those recorded with other intravenous anesthetics.

Key Words: ANESTHETICS, INTRAVENOUS—propofol. INDUCTION, ANESTHETIC—propofol.

Propofol (2,6 diisopropyl phenol) is a short-acting intravenous anesthetic. The pharmacokinetic profile of the original formulation (1–3), which used Cremophor EL as the solubilizing agent, suggested that it might be suitable for continuous infusion anesthesia. This suggestion was substantiated (4). Hemodynamic values were found to be similar to those recorded during infusion of other intravenous anesthetics under comparable conditions (5). To obviate problems associated with Cremophor EL, propofol has been reformulated as an aqueous emulsion (1% propofol, 10% soya bean oil, 2.25% glycerol, and 1.2% egg phosphatide). The dose required for the induction of anesthesia in unpremedicated patients is 20% greater than for the original formulation (6). The demonstration of altered pharmacodynamics indicated the need for studies to determine whether the emulsion formulation of propofol would also be suitable for infusion. Preliminary studies of the emulsion formulation (7,8) have shown the ED_{50} to be 53.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to prevent movement in response to surgical incision in patients premedicated with morphine and breathing 67% nitrous oxide.

We have studied hemodynamic responses to the induction of anesthesia with the emulsion formulation of propofol and subsequent responses during surgery in otherwise healthy patients anesthetized with nitrous oxide supplemented by an infusion of propofol at either 54 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or 108 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Patients were studied during both spontaneous and controlled ventilation.

Methods

The study was approved by the Committee on Safety of Medicines and the Bristol Health District Ethics Committee. Having been given a careful explanation

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Presented in part at The 6th Annual Scientific Meeting of the European Academy of Anaesthesiology, Basel, Switzerland, September 1985.

Received from the Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary, Bristol, United Kingdom. Accepted for publication August 6, 1986.

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of the purpose and nature of the study, each patient freely consented to participate. Normotensive patients (ASA I or II) scheduled for body surface surgery were randomly allocated to group 1 (propofol infusion rate: 54 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or group 2 (108 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Group 1 consisted of six men and three women having a mean age (±SD) of 47.7 ± 7.7 yr, and group 2 consisted of four men and four women having a mean age (±SD) of 47.3 ± 5.6 yr.

All patients were premedicated with intramuscular morphine sulfate, 0.15 mg/kg, 1 hr before the study began. Intravascular access was established under local anesthesia with a 16-gauge cannula in a vein on the dorsum of the hand or wrist, an 18-gauge Teflon cannula in a brachial artery, and a 70-cm catheter (Drumcath, Abbott Laboratories) advanced from a cubital vein to the right atrium, as assessed by pressure waveform monitoring. Propofol was given through the peripheral venous cannula; no other drugs were given by this route. The arterial and central venous catheters were connected to Gould-Statham P23Ia transducers and their outputs amplified by Hewlett-Packard 78205 modules and recorded on an ink-jet recorder (Siemens-Elema EM81). The electrocardiogram was recorded from three leads in the CM5 configuration. Intermittent measurement of cardiac output was made by the indocyanine green dye dilution method (9), and standard formulas were used to derive stroke volume and systemic vascular resistance (SVR). Values for cardiac output ($\dot{Q}_{70}$) and stroke volume (SV_{70}) were standardized for 70 kg body weight. Immediately after each cardiac output measurement, arterial blood samples were taken for determination of P_{CO_2}, P_{O_2}, and pH using an ABL3 blood gas analyzer (Radiometer, Copenhagen). End-tidal carbon dioxide was measured continuously during anesthesia (Gould Capnograph Mk II).

After insertion of the catheters, time sufficient to assure hemodynamic stability was allowed to pass before awake values were recorded. Anesthesia was then induced by an injection of propofol, 2 mg/kg, lasting 20 sec. A continuous infusion of propofol, delivered by calibrated syringe pump (Vickers Treonic IP3), was started immediately at either 54 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (group 1) or 108 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (group 2). The rate remained unaltered throughout the study and no supplementary doses were given to any patient. The occurrence and duration of apnea were recorded. Patients breathed nitrous oxide, 67%, in oxygen from a Mapleson A system connected to a face mask. The fresh gas ratio was constant throughout the study. The ECG, heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and central venous pressure (CVP) were recorded continuously. Cardiac output was remeasured 3 min after the induction dose of propofol had been given. Samples of arterial blood (2 ml) were taken at intervals throughout the study for measurement of whole blood propofol concentration by high pressure liquid chromatography with fluorescence detection, in a modification of the method of Adam et al. (10).

Succinylcholine, 1 mg/kg, was given through the central venous catheter 9 min after induction. The trachea was intubated with a tube that had been generously lubricated with 5% lidocaine ointment. The maximum hemodynamic response to intubation was recorded. A short period of controlled ventilation was subsequently required pending the resumption of spontaneous breathing. The next cardiac output measurements (SVNS) were made 30 min after the induction of anesthesia, but before surgery, with the patient undisturbed and breathing spontaneously.

Responses to the initial surgical incision were recorded and, if the patient did not move, cardiac output was measured 15 min later (SVS). Intermittent positive pressure ventilation (IPPV) was then established using a Penlon-Oxford ventilator situated in a circle system without a carbon dioxide absorber (11). The ventilator was adjusted to deliver a tidal volume 12–15 ml/kg at a frequency of 12 breaths per minute. In five patients (group 1, $n = 4$; group 2, $n = 1$) succinylcholine 0.3 mg/kg was required to achieve the transition to IPPV. The fresh gas flow was adjusted to maintain the end-tidal CO_2 at 4.8–5.4%.

If the patient moved in response to the initial incision (group 1, $n = 3$; group 2, $n = 1$), the surgeon was asked to stop surgery for 1 min. If movements persisted on the resumption of surgery (group 1, $n = 3$), the SVS measurements were made immediately, a supplementary dose of succinylcholine was given and IPPV established. The final measurement of cardiac output was made, in all patients, when ventilation had been controlled for 30 min (IPPVS).

During the final stages of the operation, spontaneous ventilation was encouraged by reducing the fresh gas flow and allowing the end-tidal CO_2 to reach 6.5%. At the conclusion of surgery, the propofol infusion and nitrous oxide were discontinued simultaneously, the trachea was extubated and the patient allowed to breathe oxygen-enriched air from a face mask. The times were recorded from the discontinuation of the anesthetic to 1) the first response to command ("open your eyes") and 2) recall of birthdate. The vein used for the administration of propofol was examined for signs of phlebitis and/or thrombosis immediately after surgery and again 24 hr later. Patients were questioned about their experience during induction, maintenance and recovery with specific at-

Table 1. Anesthetic Details of Patients Receiving Propofol by Infusion

	Group 1 (n = 9)	Group 2 (n = 8)
Apnea on induction[a] (sec)	62.9 ± 18.3	77.0 ± 20.7
Movement in response to surgery	n = 3	n = 1
Movement in response to IPPV	n = 4	n = 1
Duration of anesthesia[a] (min)	122.7 ± 27.3	127.0 ± 35.1
Total dose propofol[a] (mg)	717.4 ± 194.2	1086.8 ± 459.8
Recovery times from the end of infusion (min)		
To eyes open[b]	4.51 (2–11)	5.86 (4–14)
To recall of birthdate[b]	9.75 (5–19)	13.33 (9–23)

[a] Mean ± SD.
[b] Median and range.

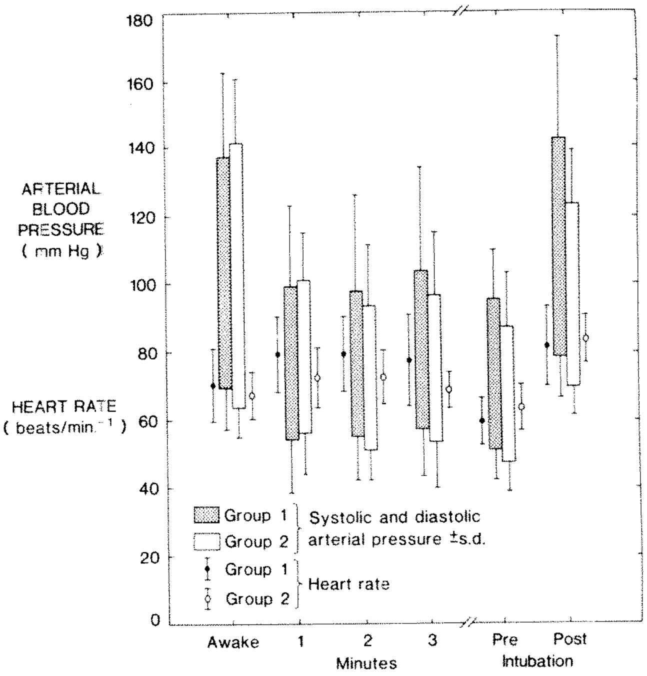

Figure 1. Hemodynamic response to induction of anesthesia with propofol 2 mg/kg and to the subsequent maintenance with an infusion of propofol at 54 or 108 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to supplement nitrous oxide (67%) anesthesia. Values shown were recorded during the first 3 min of anesthesia, before laryngoscopy (at 9 min) and after endotracheal intubation (peak response).

tention to the possibility of awareness. Blood loss did not exceed 150 ml in any patient, and insensible fluid losses were not replaced.

The data were analyzed for normality of distribution. Mann–Whitney U-tests, repeated measures analysis of variance and paired t-tests with correction for the Bonferroni inequality (12,13), and correlation analysis were used where appropriate. The recovery times were found to be skewed and analysis was performed on log-transformed data. Results are given as mean ± SD except where specified.

Results

Patients in the two groups were similar with respect to age and weight (Mann-Whitney U-tests: $P > 0.05$). Discomfort in the arm was reported, at the time of induction, by five patients (30%) and was variously described as a cold sensation, tingling, warmth, or severe burning. Induction of anesthesia was satisfactory in all patients after the injection of propofol, 2 mg/kg, although transient apnea occurred in every patient (Table 1).

Induction and Early Maintenance of Anesthesia

Awake hemodynamic values were similar in the two groups ($P > 0.05$). Figure 1 and Table 2 show the hemodynamic responses recorded during the study. There was a rapid change in arterial blood pressure: 1 min after the induction of anesthesia, SAP had decreased to 72% of the awake value in both groups ($P < 0.01$) and DAP to 79% in group 1 ($P < 0.05$) but to only 88% in group 2 (not significant). Although the changes of arterial pressure persisted during the induction sequence there were no significant changes of $\dot{Q}_{70}$, SV_{70}, HR, or SVR in either group. All patients were temporarily apneic after the induction of anesthesia (Table 1) and, compared to awake values, the arterial P_{CO_2} of both groups was persistently increased to over 50 mm Hg during spontaneous ventilation ($P < 0.001$). Systolic arterial pressure, diastolic arterial pressure, and heart rate increased in both groups ($P < 0.001$) at the time of tracheal intubation (9 min), but did not significantly exceed preoperative values (Fig. 1).

Maintenance Anesthesia and Surgery

The duration of infusion and total dose of propofol are shown in Table 2. The hemodynamic response to laryngoscopy was transient and 30 min after induction, with the patients unstimulated and breathing spontaneously (SVNS), a clinically stable level of anesthesia had been attained. In group 1, SAP and DAP at SVNS did not differ significantly from 3-min

Table 2. Hemodynamic Changes Associated with Induction and Maintenance of Anesthesia

	Awake		3 min		SVNS		SVS		IPPVS	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Systolic arterial pressure (mm Hg)	136.9 ± 25.4	141.0 ± 18.8	103.8^{a} ± 30.8	96.3^{c} ± 18.7	89.0^{c} ± 16.3	77.3^{c} ± 13.9	98.0^{b} ± 19.9	87.1^{c} ± 17.7	109.4 ± 33.7	90.9^{c} ± 19.8
Diastolic arterial pressure (mm Hg)	68.6 ± 11.3	63.5 ± 8.7	56.7 ± 13.6	53.0 ± 13.2	49.0^{b} ± 10.2	41.4^{c} ± 7.1	53.8^{a} ± 11.4	51.8^{a} ± 11.5	61.0 ± 15.0	53.5 ± 10.1
Heart rate (beat/min)	69.7 ± 11.0	67.4 ± 9.2	77.0 ± 14.4	68.8 ± 5.9	60.7 ± 8.2	62.8 ± 6.0	61.7 ± 7.3	64.5 ± 8.4	59.9^{a} ± 5.6	62.1 ± 11.1
Central venous pressure (mm Hg)	5.3 ± 3.8	4.7 ± 3.1	6.3 ± 3.3	4.1 ± 2.9	7.9 ± 4.8	4.2 ± 4.0	7.7 ± 3.6	4.6 ± 4.0	7.2 ± 3.6	4.8 ± 2.8
Cardiac output (L·min^{-1}·70kg^{-1})	6.83 ± 2.60	7.05 ± 1.94	6.08 ± 2.31	6.08 ± 1.59	4.66^{a} ± 1.48	5.19 ± 1.78	4.37^{b} ± 1.16	4.78^{b} ± 1.08	3.57^{c} ± 0.89	3.73^{c} ± 0.99
Stroke volume (ml/70 kg)	95.6 ± 23.9	101.5 ± 20.3	78.1 ± 21.7	88.1 ± 19.7	77.3 ± 18.7	81.8 ± 21.9	69.4^{a} ± 16.9	74.8^{a} ± 16.0	63.4^{b} ± 22.2	60.1^{c} ± 12.7
Systemic vascular resistance (dyn·s·cm^{-5})	937 ± 262	1063 ± 286	805 ± 235	879 ± 195	830 ± 189	840 ± 153	993 ± 285	1027 ± 221	1391^{a} ± 406	1381^{a} ± 180
Arterial P_{CO_2} (mm Hg)	39.4 ± 4.5	39.3 ± 3.1	50.7^{c} ± 3.2	47.9^{b} ± 5.3	52.8^{c} ± 5.9	52.4^{b} ± 8.2	53.4^{c} ± 6.6	52.3^{b} ± 8.9	41.0 ± 3.2	38.4 ± 5.3
Whole blood propofol (μg/ml)	0	0	—	—	2.03 ± 0.24	4.16 ± 0.74	2.13 ± 0.32	4.14 ± 0.51	2.17 ± 0.26	4.33 ± 0.58

All values are mean ± SD (paired *t*-test).

Abbreviations: SVNS, 30 min after induction with spontaneous ventilation; SVS, during surgery with spontaneous ventilation; IPPVS, during surgery with controlled ventilation.

Induction, propofol 2 mg/kg.

Maintenance, propofol infusion to supplement nitrous oxide, 67%.

[a] $P < 0.05$, compared to awake value.

[b] $P < 0.01$, compared to awake value.

[c] $P < 0.001$, compared to awake value.

values, and were, respectively, 65% and 71% of the values recorded with the patient awake ($P < 0.001$). However, in group 2, the decreases of SAP and DAP from 3 min to SVNS were significant ($P < 0.01$), and the values were 55% and 65%, respectively, of those recorded awake ($P < 0.001$). Cardiac output ($\dot{Q}_{70}$) decreased significantly ($P < 0.05$) in group 1 but not in group 2, and the concomitant changes of SV_{70} and SVR were not significant in either group. Arterial P_{CO_2} remained above awake values in both groups ($P < 0.001$). No patient was hypoxemic at any stage.

The three patients in group 1 who had responded to the first surgical incision continued to do so when the surgeon resumed stimulation after pausing for 1 min. The SVS measurements in these patients were made within 5 min of the first incision. The one patient in group 2 that had responded settled spontaneously and all the SVS measurements in that group were made 15 min after the first incision. The subsequent decreases below SVNS levels of $\dot{Q}_{70}$ and SV_{70} and the increases in SAP, DAP, HR, and SVR associated with surgery (SVS) did not reach statistical significance in either group ($P > 0.05$). However, in both groups at SVNS the change from awake values of $\dot{Q}_{70}$ and SV_{70}, but not SVR, was significant ($P < 0.05$). Arterial P_{CO_2} did not decrease in response to the surgical stimulus. In both groups the introduction of positive pressure ventilation during surgery (IPPVS) was associated with a decrease of arterial P_{CO_2} to the awake value and an increase in SVR, compared to the SVS stage ($P < 0.01$). Despite these changes, the differences in SAP, DAP, $\dot{Q}_{70}$, and SV_{70} recorded between SVS and IPPVS did not reach statistical significance in either group. The hemodynamic and arterial P_{CO_2} values were not significantly different between groups (ANOVA).

Whole blood propofol concentrations during the three stages SVNS, SVS, and IPPVS are shown in Table 2. Assuming steady state pharmacokinetic conditions at the times that these measurements were made, one can derive mean values for the clearance in each stage (infusion rate/whole blood concentration) to be between 24.9 and 26.6 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ (range 21.1–37.7 min).

There was no correlation between the total dose of propofol given and the log-transformed recovery times, although group 1 values for the former were less than those for group 2 ($P < 0.01$). No evidence of venous thrombosis or phlebitis was discovered in any patient within 24 hr of the infusion of propofol. None of the patients, including those who had moved in response to the first incision or the introduction of IPPV, had any recall of these events or suggestion of awareness during the procedure.

Discussion

The study shows that the emulsion formulation of propofol is suitable for induction of anesthesia and for maintenance of anesthesia when given by continuous infusion to supplement nitrous oxide (67%). The hemodynamic response to an infusion of either 54 or 108 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ was satisfactory. To allow logical comparison of the response to intravenous infusions of different anesthetics an ED_{50}, the minimum infusion rate (MIR), was introduced (14). It is the corollary of minimum alveolar concentration (MAC) for inhalational anesthetics (15,16).

The efficacy defined by both MAC and MIR is the same: the dose required to prevent movement to surgical incision in 50% of patients. It is therefore justifiable to make comparisons of equipotent doses of these two types of anesthetics (5). An important premise is that a steady pharmacologic state has been achieved. This occurs more rapidly with inhalational than with intravenous anesthetics. The inhalation of a volatile anesthetic in multiples of MAC correlates with proportional increments in blood concentration within a short time whereas, for example, doubling the infusion rate of an intravenous anesthetic does not immediately result in a doubling of blood concentration. The relationships between the whole blood propofol concentrations in the two groups of patients in the present study and the fact that the derived values for clearance (approximately 1.8 L/min) were similar to those derived from single-dose elimination studies (17,18) implies that we had achieved a near steady state of infusion by the time the measurements at the three later stages (SVNS, SVS, and IPPVS) were made. The detailed pharmacokinetic results derived from the present study of the emulsion formulation (Prys-Roberts, Cockshott, and Douglas, unpublished observations) confirm that blood propofol concentrations achieved after 30 min infusion were within 10–15% of those subsequently achieved during further periods of anesthesia (stages SVNS, SVS, IPPVS). The ED_{50} infusion rate for an intravenous anesthetic provides a logical and useful starting point for the investigation and comparison of hemodynamic and other effects of intravenous anesthetics (5).

Factors other than the rate of infusion influence the ED_{50}. These include premedication, the nitrous oxide concentration of the inspired gas, and patient age (19). Comparisons using the ED_{50} (MIR) concept have been made previously for Althesin (20), minaxolone (21), methohexital (22), and the Cremophor EL formulation of propofol (4).

Despite the fact that the dose required for induction of anesthesia is greater for the emulsion than for the

Cremophor EL formulation of propofol (6), the ED_{50} for both is similar (7): 53.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (emulsion) and 51.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (Cremophor EL). This result can be explained by the distribution of active drug being similar for both formulations at what approaches a steady state.

As the program for the present study was similar to that used to investigate the infusions of other intravenous anesthetics, it is possible to make comparisons between them. In particular, it is interesting to compare the two different formulations of propofol (4) and methohexital (22), the only other currently available intravenous anesthetic suitable for use by infusion. From similar awake values (all studies), the decrease in SAP associated with the infusion of the emulsion formulation of propofol was greater than with the Cremophor EL formulation or methohexital ($P < 0.05$, unpaired *t*-tests) at all stages (3 min, SVNS, SVS, IPPVS). However, $\dot{Q}_{70}$ decreased to similar values for the three drugs at all stages. Heart rates during the infusion of the emulsion formulation of propofol were less ($P < 0.05$) at all stages than those during infusion of the Cremophor EL formulation, and in particular, heart rate did not increase with the first incision in patients receiving the emulsion as it had with the Cremophor EL formulation. The ventilatory depression caused by the three drugs is similar. An ED_{50} infusion of methohexital did not prevent a marked hemodynamic response to laryngoscopy and tracheal intubation (22), whereas both formulations of propofol partially obtunded the response to the extent that peak values were not significantly different from those recorded awake.

In view of the ED_{50} of the emulsion formulation of propofol (8), it was not surprising that three of the nine patients receiving propofol, 54 $\mu g \cdot kg^{-1} \cdot min^{-1}$, in the present study responded to the surgical incision, 30 min after induction. Anesthesia was more easily maintained with propofol, 108 $\mu g \cdot kg^{-1} \cdot min^{-1}$; the patient who responded to incision and the introduction of IPPV subsequently settled satisfactorily. The ideal infusion rate would probably be close to 108 $\mu g \cdot kg^{-1} \cdot min^{-1}$; the ED_{95} for the emulsion formulation of propofol is 112.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (8), and the hemodynamic consequences of increasing the rate of infusion of intravenous anesthetics are not so great as those of similar increments of volatile anesthetics (5). However, particular caution is necessary in patients with coronary artery disease (23). Also, the effects of other drugs, such as opioids, can significantly influence the response to continuous infusion anesthesia. The administration of fentanyl to patients receiving an infusion of the Cremophor EL formulation alters the pharmacokinetics of propofol (Prys-Roberts and Adam, unpublished observations) and further work with the emulsion formulation of propofol given with fentanyl is necessary.

A noticeable feature in both groups in the present study was the rapid recovery. Many patients remarked on their "clear-headedness" prior to returning from the recovery room to the general ward. The infusion of propofol was not associated with any adverse side effects.

The emulsion formulation of propofol provides a useful addition to the small number of intravenous anesthetics that are suitable for use by continuous infusion. It has the advantage that, unlike the barbiturates, prolonged recovery is not a feature of its use. Further investigation of the emulsion formulation of propofol, particularly its use by computer-controlled infusion, should be undertaken when its pharmacokinetic profile has been fully established. It should be possible to decrease the time required to achieve a steady state by BET infusion (24), which minimizes the peak initial effect caused by an induction dose and avoids the after-fall that occurs before a fixed rate infusion has achieved the desired blood concentration.

We are grateful to Mr. J. Dye for technical assistance during the study and to Dr. R. D. Stark and Miss S. Binks of ICI Pharmaceuticals Division, Macclesfield, Cheshire, UK for support of the study; also to Dr. I. Cockshott and Mr. E. J. Douglas (also of ICI Pharmaceuticals Division) who performed the measurements of blood propofol concentrations. We also thank Mr. R. N. Baird, FRCS, Mr. M. J. Horrocks, FRCS, Mr. N. J. McC. Mortensen, FRCS, and Professor R. C. N. Williamson, FRCS, consultant surgeons at the Bristol Royal Infirmary who allowed us to study patients under their care.

References

1. Adam HK, Glen JB, Hoyle PA. Pharmacokinetics in laboratory animals of ICI 35868, a new i.v. anaesthetic agent. Br J Anaesth 1980;52:743–6.
2. Adam HK, Kay B, Douglas EJ. Blood diisopropyl phenol levels in anaesthetised patients. Anaesthesia 1982;37:536–40.
3. Adam HK, Briggs LP, Bahar M, Douglas EJ, Dundee JW. Pharmacokinetic evaluation of ICI 35868 in man. Br J Anaesth 1983;55:97–102.
4. Prys-Roberts C, Davies JR, Calverley RK, Goodman NW. Haemodynamic effects of infusions of diisopropyl phenol (ICI 35868) during nitrous oxide anaesthesia in man. Br J Anaesth 1983;55:105–11.
5. Prys-Roberts C. Cardiovascular effects of continuous intravenous anaesthesia compared with those of inhalational anaesthesia. Acta Anaesthesiol Scand 1982;26(suppl 75):10–7.
6. Cummings GC, Dixon J, Kay NH, et al. Dose requirements of ICI 35,868 (propofol, 'Diprivan') in a new formulation for the induction of anaesthesia. Anaesthesia 1984;39:1168–71.
7. Coates DP, Prys-Roberts C, Spelina KR, Monk CR, Norley I. Propofol ('Diprivan') by intravenous infusion with nitrous ox-

ide: dose requirements and haemodynamic effects. Postgrad Med J 1985;61(suppl 3):76–9.

8. Spelina KR, Coates DP, Monk CR, Prys-Roberts C, Norley I. Dose requirements of propofol by infusion during nitrous oxide anaesthesia. 1: Patients premedicated with morphine sulphate. Br J Anaesth 1986;58:1080–4.
9. Prys-Roberts C, ed. Measurement of cardiac output and regional blood flow. In: The circulation in anaesthesia. Oxford: Blackwell Scientific Publications, 1980:531–60.
10. Adam HK, Douglas EJ, Plummer GF, Cosgrove MB. Estimation of ICI 35,868 (Diprivan) in blood by high performance liquid chromatography, following coupling with Gibb's reagent. J Chromatogr 1981;223(Biomed Appl 12):232–7.
11. Suwa K, Yamamura H. The effect of gas inflow on the regulation of CO_2 levels with hyperventilation during anesthesia. Anesthesiology 1970;33:440–8.
12. Glantz SA. Primer of biostatistics. New York: McGraw-Hill, 1981:87–8.
13. Anonymous. Minitab reference manual. Boston: Duxbury Press 1981.
14. Sear JW, Prys-Roberts C. Plasma alphaxalone concentrations during continuous infusions of Althesin. Br J Anaesth 1979;51:861–5.
15. Quasha AL, Eger EI, Tinker J. Determination and applications of MAC. Anesthesiology 1980;53:315–34.
16. Hickey RF, Eger EI. Circulatory effects of inhaled anaesthetics. In: Prys-Roberts C, ed. The circulation in anaesthesia. Oxford: Blackwell Scientific Publications, 1980:441–57.
17. Briggs LP, White M, Cockshott ID, Douglas EJ. The pharmacokinetics of propofol ('Diprivan') in female patients (Abstract). Postgrad Med J 1985;61(suppl 3):58–9.
18. Kay NH, Uppington J, Sear JW, Douglas EJ, Cockshott ID. Pharmacokinetics of propofol ('Diprivan') as an induction agent. Postgrad Med J 1985;61(suppl 3):55–7.
19. Sear JW, Prys-Roberts C, Phillips KC. Age influences the minimum infusion rate (ED_{50}) for continuous infusions of Althesin and methohexitone. Europ J Anaesthesiol 1984;1:319–25.
20. Sear JW, Prys-Roberts C. Dose related haemodynamic effects of continuous infusions of Althesin in man. Br J Anaesth 1979;51:867–73.
21. Sear JW, Prys-Roberts C, Gray AJG, Walsh EM, Curnow JSH, Dye J. Infusions of minaxolone to supplement nitrous oxide–oxygen anaesthesia. A comparison with Althesin. Br J Anaesth 1981;53:339–50.
22. Prys-Roberts C, Sear JW, Low JM, Phillips KC, Dagnino J. Hemodynamic and hepatic effects of methohexital infusion during nitrous oxide anesthesia in man. Anesth Analg 1983;62:317–23.
23. Williams JP, McArthur JD, Walker WE, Teunissen E, Rietsema K, Stanley TH. The cardiovascular effects of propofol in patients with impaired cardiac function. Anesth Analg 1986;65:S166.
24. Schwilden H, Stoeckel H, Schuttler J, Lauven PM. Pharmacological models and their use in clinical anaesthesia (special review). Eur J Anaesth 1986;3:175–208.

Comparative Maternal, Fetal, and Neonatal Effects of Chloroprocaine with and without Epinephrine for Epidural Anesthesia in Obstetrics

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ABBOUD TK, DERSARKISSIAN L, TERRASI J, MURAKAWA K, ZHU J, LONGHITANO M. Comparative maternal, fetal, and neonatal effects of chloroprocaine with and without epinephrine for epidural anesthesia in obstetrics. Anesth Analg 1987;66:71–5.

The effects of epidural chloroprocaine with and without 1:200,000 epinephrine during labor and delivery on uterine activity, progress of labor, fetal heart rate, maternal blood pressure, newborn Apgar scores, neonatal acid–base status, and the Neurologic and Adaptive Capacity Scoring System (NACS) were compared in 28 parturients. Patients in group I (n = 14) received 2% chloroprocaine with 1:200,000 epinephrine and patients in group II (n = 14) received 2% plain chloroprocaine. Addition of epinephrine to chloroprocaine had no significant effects on uterine activity, duration of first or second stages of labor, or fetal heart parameters. Apgar scores, neonatal acid–base status, and the NACS were equally good in the two groups. Duration of analgesia was significantly longer in group I than in group II patients (76 ± 3.8 vs 42.9 ± 1 min, P < 0.001). We conclude that addition of epinephrine to chloroprocaine during epidural anesthesia in the normal parturient has no adverse effects on mother, fetus, neonate, or the progress of labor and that it significantly prolongs the duration of anesthesia.

Key Words: ANESTHESIA—obstetrics. ANESTHETIC TECHNIQUES—epidural. LOCAL ANESTHETIC—chloroprocaine.

The addition of epinephrine to local anesthetics (5 μg/ml) decreases vascular absorption of local anesthetics (1–4) and improves the quality and the duration of anesthesia (5–7). However, its use for epidural anesthesia in obstetrics remains controversial, mainly due to the possible adverse effects of epinephrine on uterine activity, uterine blood flow, and maternal and fetal cardiovascular parameters.

We have recently reported that the addition of epinephrine to lidocaine (8) or bupivacaine (9) significantly prolonged the duration of epidural anesthesia during labor without adversely affecting the mother or the neonate.

The present study was undertaken to determine the effects on the mother, the fetus, and the neonate of epinephrine added to chloroprocaine during epidural analgesia.

Materials and Methods

Twenty-eight parturients at term with no obstetric or medical complications who elected to have epidural anesthesia for labor and delivery were studied. The study was approved by the Committee on Human Experimentation, and informed consent was obtained from all patients. All patients had ruptured membranes. Utilizing a Corometric 112 fetal monitor, uterine activity was monitored with a transcervical intrauterine catheter, and fetal heart rate (FHR) was directly monitored with a scalp electrode. Before induction of epidural anesthesia, all fetuses had normal FHR patterns.

With patients in the left lateral decubitus position, epidural catheters were placed at L3–4 interspace and advanced 2 cm cephalad. Patients were kept in the lateral position and were encouraged to remain in the same position throughout the study. All patients were given 500 ml of 5% dextrose in lactated Ringer's solution and, after measurement of FHR, uterine activity, maternal blood pressure and heart rate for 30 min, patients were randomly given one of two local anesthetic solutions.

Patients in group I (n = 14) received 2% chloro-

Received from the Department of Anesthesiology, Los Angeles County–University of Southern California Medical Center, Los Angeles, California. Accepted for publication August 1, 1986.

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Table 1. Patient Data

	Chloroprocaine with epinephrine (group I, n = 14)	Chloroprocaine alone (group II, n = 14)
Maternal age[a] (yr)	21.3 ± 0.9	24.7 ± 1.6
Maternal weight[a] (kg)	67.3 ± 2.7	74.7 ± 2
Maternal height[a] (cm)	156.4 ± 0.7	161.8 ± 2
Parity		
Primiparous	9	7
Multiparous	5	7
Gestational age[a] (wk)	40.1 ± 0.5[b]	38.8 ± 0.4
Infant weight[a] (gm)	3408.8 ± 132	3281.3 ± 133

[a] Values are mean ± SEM.
[b] $P < 0.05$ using Student's t-test.

Table 2. Clinical Data

	Chloroprocaine with epinephrine (group I, n = 14)	Chloroprocaine alone (group II, n = 14)
Total amount of drug[a] (mg)	497.4 ± 80	588.9 ± 114
Number of patients with hypotension	0	0
Duration of[a]		
Block (min)	76.4 ± 3.8[b]	42.9 ± 1
First stage (min)	295.8 ± 44	444.6 ± 106
Second stage (min)	61.4 ± 7	67.6 ± 17
Mode of delivery		
Spontaneous	11	11
Forceps	0	0
Cesarean	3	3

[a] Values are mean ± SEM.
[b] $P < 0.001$

procaine with 1:200,000 epinephrine, those in group II (n = 14) received 2% chloroprocaine alone. If, 5 min after a test dose of 3 ml of local anesthetic was injected, there was no evidence of subarachnoid injection, the remainder of the local anesthetic was injected. The dose was chosen to provide analgesia to a level of T-10.

Local anesthetic was reinjected as clinically indicated and observations continued until delivery of the infant. Duration of analgesia after each loading dose of the local anesthetic was defined as the time from onset of pain relief until the time of onset of discomfort. The overall quality of analgesia was evaluated using our routine scale ranging from 0 for no pain relief to 4+, representing excellent analgesia.

Maternal hypotension was considered to be present whenever systolic blood pressure decreased more than 30 torr or to less than 100 torr. Hypotension was corrected by increasing the rate of intravenous fluid infusion and by intravenous administration of ephedrine. Duration of first and second stages of labor and the mode of delivery were noted.

Neonates were evaluated by Apgar scores at 1 and 5 min, by umbilical venous and arterial blood acid base status, and by the Neurologic and Adaptive Capacity Scoring System (NACS) 15 min, 2 hr, and 24 hr after birth, according to a previously described protocol (10). Apgar scores were assigned by pediatricians who were unaware of the local anesthetic administered. The NACS examination was performed by a trained anesthesia research fellow. The NACS gives a numerical score, with a maximum of 40. Arbitrarily choosing 35–40 as the score denoting a vigorous baby (9), we determined the percentages of infants scoring 35 or higher and compared these in each group at 15 min, 2 hr, and 24 hr after birth. We also determined the percentage of infants having high scores on each of the individual test items. Persons who evaluated FHR patterns, uterine activity, and the neonate were unaware of the local anesthetic administered.

Data were analyzed for statistical significance using Student's t-test and χ^2-analyses when appropriate. A P value of less than 0.05 was considered statistically significant.

Results

Data on maternal age, weight, height, parity, infant's gestational age, and weight are summarized in Table 1. There were no significant differences between the two groups with the unimportant exception that gestational age was slightly higher in group I compared to group II.

Effects on the Mother

Clinical results are shown in Table 2. None of the patients in either group developed hypotension. The quality of analgesia was either 3+ or 4+ in all patients in both groups. Duration of analgesia was significantly longer in group I patients than in group II patients ($P < 0.001$). Duration of first and second stages of labor as well as the mode of delivery did not differ significantly in the two groups of patients.

Effects on Uterine Activity and Fetal Heart Rate

Uterine activity as measured by Montevideo units did not change significantly in the two groups (Fig. 1). Montevideo unit is defined as the product of the av-

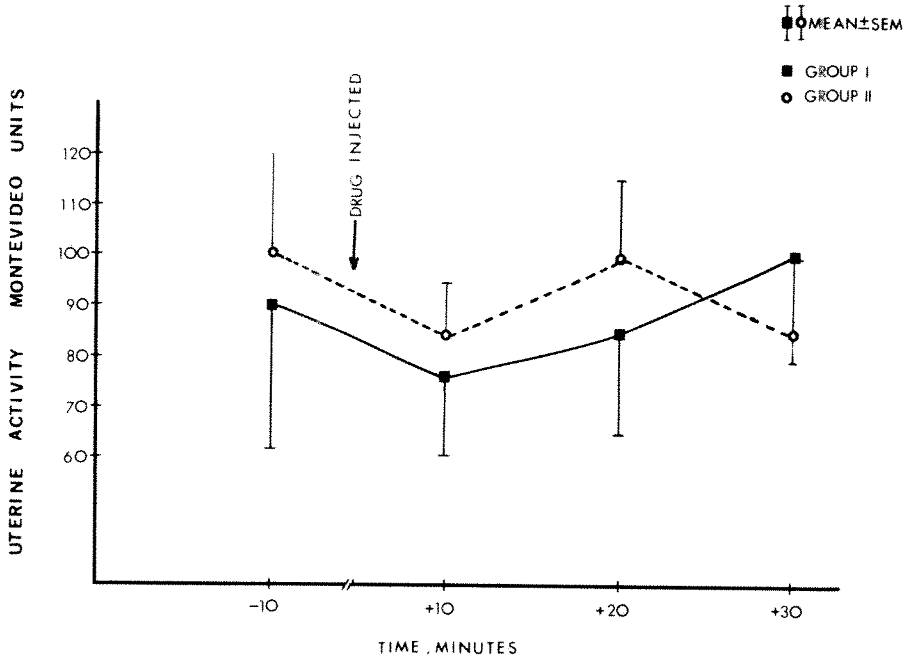

Figure 1. Effects of epidural anesthesia on uterine activity (mean ± SEM) in group I ($n = 14$) and group II ($n = 14$). No changes were statistically significant by Student's t-test.

Table 3. Acid–Base and Blood Gas Data

	Chloroprocaine with epinephrine (group I, $n = 14$)	Chloroprocaine alone (group II, $n = 14$)
Umbilical vein		
Number	12	8
pH	7.30 ± 0.02	7.36 ± 0.02
Po_2 (torr)	25.92 ± 1.54	26.88 ± 3.20
Pco_2 (torr)	39.67 ± 2.56	38.38 ± 1.76
Base excess (mEq/L)	−6.08 ± 0.53	−5.63 ± 0.78
Umbilical artery		
Number	12	8
pH	7.25 ± 0.02	7.29 ± 0.02
Po_2	23.25 ± 1.69	20.75 ± 2.42
Pco_2	44.17 ± 2.61	43.38 ± 2.81
Base excess (mEq/L)	−6.42 ± 0.74	−5.75 ± 0.84

Values are mean ± SEM; no significant difference between groups as determined by Student's t-test.

Table 4. Percentage of NACS Scores of 35–40 for Infants Whose Mothers Received Chloroprocaine with Epinephrine (Group I) and for those Whose Mothers Received Plain Chloroprocaine (Group II)

2 hr		24 hr	
Group I ($n = 14$)	Group II ($n = 10$)	Group I ($n = 14$)	Group II ($n = 10$)
86	80	93	90

No significant differences between groups by χ^2-test.

erage amplitude of uterine contraction (in mm Hg) multiplied by the number of contractions in 10 min. None of the fetuses in either group had any significant abnormal heart rate patterns as defined by Kubli et al. (11).

Effects on the Newborn

All neonates were vigorous at 5 min. Two neonates in group I had low 1-min Apgar scores of 4 and 6. One neonate in group II had a score of 6. These incidences were not significantly different.

Umbilical Artery and Vein Blood Acid–Base Status

Umbilical arterial and venous acid–base status was within normal limits in the two groups (Table 3).

Neurologic and Adaptive Capacity Scores

The NACS scores of the two groups of neonates are presented in Table 4. The NACS was determined only in babies whose mothers had normal spontaneous or low forceps deliveries. There were no significant differences between the two groups in test scores for any test item on the NACS. The percentage of infants who scored 35–40 on the NACS was not significantly different between the two groups.

Discussion

Epidural anesthesia during labor using lidocaine with epinephrine (8) or bupivacaine with epinephrine (9) has been shown to be safe for both mother and neonate. However, to date there has not been a detailed comparative study to evaluate the effects of epidural chloroprocaine with and without epinephrine on the forces of labor, duration of the first and second stages of labor and the mode of delivery. Findings from our study demonstrate that addition of epinephrine to chloroprocaine does not decrease uterine activity, prolong the first or the second stages of labor, or increase the incidence of instrumental deliveries. The present findings contradict findings reported by others. In 1925 Rucker (12), for example, found that caudal anesthesia using local anesthetics with epinephrine (330 μg) decreased or abolished uterine activity, whereas there was no effect on labor when the epinephrine was omitted. Similarly, Gunther and Bauman (13) and Gunther and Bellville (14) showed that during continuous caudal anesthesia the first stage of labor was longer in parturients receiving solutions of lidocaine or mepivacaine with epinephrine (100–125 μg) than in patients given these solutions without epinephrine. Intramuscular (200–550 μg) (15) as well as intravenous (2.5–5 μg) (16) epinephrine has also been shown to diminish uterine activity. Recently, various studies of the effects of lidocaine with and without 1:200,000 epinephrine on the forces of labor demonstrated a transient decrease in uterine activity in the groups receiving epinephrine (17–19). The relatively small dose of epinephrine used in our study (40 μg) might have been a factor accounting for the observed difference in the results of our study and those reported in other studies. Bromage (20) has also suggested that uterine activity is not likely to be depressed to a significant degree if volumes of anesthetic solutions injected into the epidural space are restricted to a minimum of 4–6 ml and epinephrine concentrations do not exceed 1:200,000 (30 μg) total dose.

Another important finding of our study is the lack of adverse effects of epinephrine on the neonate as determined by Apgar scores, fetal acid base status, and the NACS. There seems to be uncertainty concerning the effect of absorbed epinephrine on uterine blood flow. Studies in pregnant ewes using 50–100 μg of epinephrine have shown a decrease in uterine blood flow (21,22). However, other studies have shown stable blood flow (23). More recently, using the 133 Xe technique, Albright et al. (24) and Jouppila et al. (25,26) found no significant changes in intervillous blood flow when 40–100 μg epinephrine was added to local anesthetics for lumbar epidural anesthesia in pregnant women. It is postulated that the primary reasons for divergent results between studies are probably related to species and methodologic differences. In the present study we did not measure intervillous blood flow, but we evaluated the effects of the added epinephrine on the fetus and the neonate and found no deleterious effects.

On the basis of maternal and fetal cardiovascular parameters, progress of labor, Apgar scores, acid–base status, and the NACS we conclude that addition of 1:200,000 epinephrine to chloroprocaine during lumbar epidural anesthesia in the healthy parturient does not prolong labor or adversely affect maternal or neonatal well-being, and it does prolong the duration of analgesia. Further work may be needed to determine whether these results are applicable to high-risk patients with impaired uteroplacental blood flow.

References

1. Braid DP, Scott DB. The systemic absorption of local analgesic drugs. Br J Anaesth 1965;37:394–404.
2. Tucker GT, Moore DC, Bridenbaugh PO, Bridenbaugh LD, Thompson GE. Systemic absorption of mepivacaine in commonly used regional block procedures. Anesthesiology 1972;37:277–87.
3. Bromage PR, Robson JG. Concentrations of lignocaine in the blood after intravenous, intramuscular, epidural and endotracheal administration. Anesthesiology 1961;16:461.
4. Mather LE, Tucker GT, Murphy TM, et al. The effects of adding adrenaline to etidocaine and lignocaine in extradural anaesthesia: II. pharmacokinetics. Br J Anaesth 1976;48:989–94.
5. Hehre FW. Continuous lumbar epidural anesthesia in obstetrics. V: Double-blind comparison of 2% lidocaine and 2% prilocaine. Anesth Analg 1969;48:177–80.
6. Bromage PR. Physiology and pharmacology of epidural analgesia. Anesthesiology 1967;28:592–622.
7. Epstein BS, Banerjee SG, Coakley CS. II. Comparative effects of prilocaine and lidocaine during peridural anesthesia for obstetrics. Anesth Analg 1968;47:228–32.
8. Abboud TK, David S, Nagappala S, Costandi J, Yanagi T, Haroutunian S, Yeh SU. Maternal, fetal and neonatal effects of lidocaine with and without epinephrine for epidural anesthesia in obstetrics. Anesth Analg 1984;63:973–9.
9. Abboud TK, Sheikh-Ol-Eslam A, Yanagi T, Murakawa M, Costandi J, Zakarian M, Hoffman D, Haroutunian S. Safety and efficacy of epinephrine added to bupivacaine for lumbar epidural analgesia in obstetrics. Anesth Analg 1985;64:585–91.
10. Amiel-Tison C, Barrier G, Shnider SM, Levinson G, Hughes SC, Stephani S. A new neurologic and adaptive capacity scoring system for evaluating obstetric medications in full term newborns. Anesthesiology 1982;56:340–50.
11. Kubli FW, Hon EH, Khazin AF, Takemura H. Observations on heart rate and pH in the human fetus during labor. Am J Obstet Gynecol 1969;104:1190–206.
12. Rucker MP. The action of adrenalin on the pregnant uterus. South Med J 1925;18:412.
13. Gunther RE, Bauman J. Obstetrical caudal anesthesia: I. a randomized study comparing 1% mepivacaine with 1% lidocaine plus epinephrine. Anesthesiology 1969;31:5–19.
14. Gunther RE, Bellville JW. Obstetrical caudal anesthesia: II. a randomized study comparing 1 percent mepivacaine with 1 percent mepivacaine plus epinephrine. Anesthesiology 1972; 37:288–98.

15. Kaiser I, Harris J. The effect of adrenaline on the pregnant human uterus. Am J Obstet Gynecol 1950;59:775–84.

16. Garrett WJ. The effects of adrenaline and noradrenaline on the intact human uterus in late pregnancy and labour. Obstet Gynaec Br Comm 1954;62:586–9.

17. Craft JB, Epstein BS, Coakley CS. Effect of lidocaine with epinephrine versus lidocaine (plain) on induced labor. Anesth Analg 1972;51:243–6.

18. Matadial L, Cibils LA. The effect of epidural anesthesia on uterine activity and blood pressure. Am J Obstet Gynecol 1976;125:846–54.

19. Zador G, Nilssen BA. Low dose intermittent epidural anaesthesia with lidocaine for vaginal delivery. II. Influence of labour and foetal acid–base status. Acta Obstet Gynecol Scand 1974; (Suppl) 34:17–30.

20. Bromage PR. Epidural analgesia. Philadelphia: WB Saunders Company, 1978:529.

21. Rosenfeld CR, Barton MD, Meschia G. Effects of epinephrine on distribution of blood flow in the pregnant ewe. Am J Obstet Gynecol 1976;124:156–63.

22. Wallis KL, Shnider SM, Hicks JS, Spivey JS. Epidural anesthesia in the normotensive pregnant ewe: effects on uterine blood flow and fetal acid–base status. Anesthesiology 1976;44:481–7.

23. DeRosayro AM, Nahrwold ML, Hill AB. Cardiovascular effect of epidural epinephrine in the pregnant sheep. Reg Anesth 1981;6:4–7.

24. Albright GA, Jouppila R, Hollmen AI, et al. Epinephrine does not alter human intervillous blood flow during epidural anesthesia. Anesthesiology 1981;54:131–5.

25. Jouppila R, Jouppila P, Kuikka J, et al. Placental blood flow during caesarean section under lumbar extradural analgesia. Br J Anaesth 1978;50:275–8.

26. Jouppila R, Jouppila P, Hollmen A, et al. Effect of segmental extradural analgesia on placental blood flow during normal labour. Br J Anaesth 1978;50:563–7.

ANESTH ANALG
1987;66:76–80

Glucose Metabolism during Liver Transplantation in Dogs

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DeWOLF AM, KANG YG, TODO S, KAM I, FRANCAVILLA AJ, POLIMENO L, LYNCH S, STARZL TE. Glucose metabolism during liver transplantation in dogs. Anesth Analg 1987;66:76–80.

Arterial and hepatic venous blood levels of glucose were studied in 12 dogs during orthotopic liver transplantation performed under ketamine anesthesia without exogenous glucose administration. During the early part of surgery, arterial blood glucose levels were stable: 161 ± 12 mg/dl (mean ± SEM) after laparotomy and 183 ± 16 mg/dl 5 min before the anhepatic stage. During the anhepatic stage, arterial blood glucose levels decreased progressively to 135 ± 9 and 88 ± 8 mg/dl, 5 min in the anhepatic stage and 5 min before reperfusion of the graft liver, respectively ($P < 0.05$). Reperfusion of the graft liver resulted in an increase in arterial glucose levels to 206 ± 17 and 240 ± 24 mg/dl, 5 and 30 min after reperfusion, respectively ($P < 0.05$). Hepatic venous blood glucose levels increased after reperfusion (405 ± 37 and 346 ± 41 mg/dl, 5 and 30 min after reperfusion, respectively) and were significantly higher than in arterial blood ($P < 0.05$). Arterial plasma insulin, measured in five animals, did not change significantly during the procedure, whereas plasma glucagon levels, stable during the preanhepatic and anhepatic stages, increased steadily after reperfusion of the graft liver, from 66.1 ± 14.2 to 108.4 ± 38.1 pg/ml ($P < 0.05$). This study shows that in dogs with ketamine anesthesia mild hypoglycemia occurs during the anhepatic stage of liver transplantation without exogenous glucose administration followed by hyperglycemia on reperfusion of the graft liver, possibly secondary to the release of glucose from the donor liver.

Key Words: ANESTHESIA—liver transplantation. LIVER—transplantation. METABOLISM—glucose.

Significant improvements have been made recently in the surgical and anesthetic management of patients undergoing liver transplantation (1,2). However, understanding of glucose metabolism during liver transplantation is still incomplete. Aldrete et al. saw hypoglycemia frequently, especially during the anhepatic stage of the procedure, and advised that large amounts of exogenous glucose be administered during orthotopic liver transplantation in humans (3). They ascribed the low levels of glucose to the absence of the liver, the main producer of blood glucose. Others have reported that hypoglycemia did not occur when small amounts of exogenous glucose were administered (4,5). Tullock et al. reported that without administration of exogenous glucose other than that in transfused blood, blood glucose levels remained within an acceptable range during the preanhepatic and anhepatic stages, but that hyperglycemia of more than 200 mg/dl occurred after reperfusion of the graft liver (4).

These differences in clinical experience remain unexplained; glucose metabolism may have been different among individual recipients, and intraoperative management also may have been different. To investigate intraoperative glucose metabolism, we measured blood levels of glucose, insulin, and glucagon in healthy dogs undergoing liver transplantation without exogenous glucose infusion.

Methods

Orthotopic liver transplantation was performed in 12 adult beagle dogs, weighing between 11.0 and 14.0 kg (mean 11.9 kg). The animals fasted overnight. Anesthesia was induced and maintained with intra-

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Supported in part by research grants from the Veterans Administration; by Project Grant No. AM-29961 from the National Institutes of Health; and by Grant No. RR-00084 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health, Bethesda, Maryland.

Received from the Departments of Anesthesiology and Surgery, Presbyterian-University Hospital, University of Pittsburgh, Pittsburgh, Pennsylvania. Accepted for publication July 8, 1986.

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Table 1. Laboratory Data during Liver Transplantation in 12 Dogs

	Preanhepatic stage		Anhepatic stage		Postanhepatic stage	
Variable	I + 30 min	II − 5 min	II + 5 min	III − 5 min	III + 5 min	III + 30 min
Body temperature (°C)	36.0 ± 0.3	35.1 ± 0.2^{a}	34.2 ± 0.3^{a}	33.7 ± 0.3^{a}	32.9 ± 0.4^{a,b}	32.8 ± 0.4^{a,b}
Arterial blood						
Hematocrit (%)	44.3 ± 1.6	42.4 ± 1.8	34.2 ± 2.3^{a}	34.1 ± 1.7^{a}	28.5 ± 2.3^{a,b}	27.3 ± 1.9^{a,b}
pH	7.43 ± 0.02	7.43 ± 0.02	7.42 ± 0.02	7.34 ± 0.02^{a}	7.30 ± 0.02^{a,b}	7.23 ± 0.02^{a,b}
Pa_{CO_2} (mm Hg)	29.3 ± 1.5	27.3 ± 1.2	25.0 ± 1.5^{a}	26.4 ± 1.8^{a}	24.6 ± 1.5^{a,b}	26.5 ± 2.0^{a}
Pa_{O_2} (mm Hg)	141.1 ± 11.5	147.7 ± 12.1	148.4 ± 7.0	148.8 ± 6.7	154.7 ± 7.6^{a,b}	154.9 ± 9.5^{a,b}
Base deficit	3.7 ± 0.7	4.3 ± 0.6	6.3 ± 0.6^{a}	9.7 ± 0.8^{a}	12.8 ± 0.8^{a,b}	14.8 ± 0.8^{a,b}
Na (meq/L)	146.7 ± 0.8	146.3 ± 1.1	142.1 ± 0.8^{a,b}	144.4 ± 1.4^{a}	141.6 ± 1.3^{a,b}	142.2 ± 1.3^{a}
K (meq/L)	2.53 ± 0.08	2.60 ± 0.12	2.81 ± 0.10^{a}	2.78 ± 0.08^{a}	4.10 ± 0.27^{a,b}	3.30 ± 0.20^{a,b}
Hepatic venous blood						
pH	7.42 ± 0.02	7.40 ± 0.02	—	—	7.15 ± 0.03^{a,c}	7.14 ± 0.04^{a,c}
Pv_{CO_2} (mm Hg)	32.2 ± 1.4^{c}	32.5 ± 1.8^{c}	—	—	44.2 ± 2.8^{a,c}	44.5 ± 3.8^{a,c}
Pv_{O_2} (mm Hg)	57.8 ± 6.3^{c}	43.8 ± 2.0^{a,c}	—	—	21.4 ± 2.2^{a,c}	26.0 ± 3.2^{a,c}
Base deficit	3.3 ± 0.6	3.8 ± 0.5	—	—	12.4 ± 1.1^{a}	12.8 ± 1.3^{a,c}
Na (meq/L)	147.0 ± 0.9	145.5 ± 1.1^{a}	—	—	140.9 ± 1.1^{a}	143.2 ± 1.2^{a}
K (meq/L)	2.63 ± 0.14	2.87 ± 0.23^{c}	—	—	4.92 ± 0.50^{a,c}	3.60 ± 0.26^{a,c}

Values are mean ± SEM.
[a] Different from the values at I + 30 min.
[b] Different from the values at III − 5 min.
[c] Different from the corresponding values in arterial blood.

venous ketamine (2 mg/kg followed by 1 mg/kg every 20–30 min), plus pancuronium bromide for muscle relaxation. The dogs were mechanically ventilated with FI_{O_2} of 0.3 and end-tidal CO_2 was maintained between 4 and 5%. Femoral arterial and jugular venous catheters were inserted for blood sampling and monitoring of arterial and central venous pressures. Crystalloid solution without glucose (Plasma-Lyte A, Travenol Laboratories, Inc., Deerfield, IL) was infused at a rate of 40 ml·kg^{-1}·hr^{-1}. Dopamine was infused to maintain mean arterial pressure above 70 torr. The surgical technique has been reported elsewhere (6). Surgery in the donor and recipient was synchronized to minimize donor organ ischemic time. The operation has three stages: a preanhepatic stage (stage I), from the induction of anesthesia to hepatectomy; an anhepatic stage (stage II), from hepatectomy to reperfusion of the graft; and a postanhepatic stage (stage III), from reperfusion of the graft liver to the end of surgery. The donor organs were preserved with cold (0–4°C) lactated Ringer's solution. In all recipient dogs, venous bypass (Bio-Medicus, Inc., Minnetonka, MN) was used during the anhepatic stage of surgery to divert blood from the splenic and femoral veins to the jugular vein. The graft liver was reperfused by unclamping the portal vein and the supra- and infrahepatic inferior vena cava after the vascular anastomoses were completed. Throughout the procedure, no glucose was administered to the recipient dogs: Neither the administered electrolyte solution nor the organ preservation solution contained glucose, and no blood was transfused during the study.

In the preanhepatic stage, femoral arterial and hepatic venous blood samples were drawn 30 min after laparotomy (I + 30 min) and 5 min before the beginning of the anhepatic stage (II − 5 min). Hepatic venous blood samples were taken by venipunctures at the proximal part of the hepatic vein to avoid contamination by blood from the inferior vena cava. During the anheptic stage, arterial blood was sampled 5 min after onset (II + 5 min) and 5 min before reperfusion of the graft liver (III − 5 min). In the postanhepatic stage, arterial and hepatic venous blood samples were collected 5 min (III + 5 min) and 30 min (III + 30 min) after reperfusion of the graft liver. The blood samples were analyzed to determine glucose levels, arterial blood–gas tensions and acid–base state, hematocrit, and levels of Na and K. Blood glucose levels were determined using the glucose oxidase test (YSI model 23 A glucose analyzer, Yellow Springs Instruments Co., Yellow Springs, OH). Arterial insulin and glucagon levels were measured in five animals during the preanhepatic and postanhepatic stages using radioimmunoassay technique (Serono Diagnostics, Braintree, MA). Data are reported as mean ± SEM. Data were analyzed by analysis of variance for repeated measures (ANOVA), and specific differences were assessed with the Student–Newman–Keuls test; $P < 0.05$ was considered statistically significant.

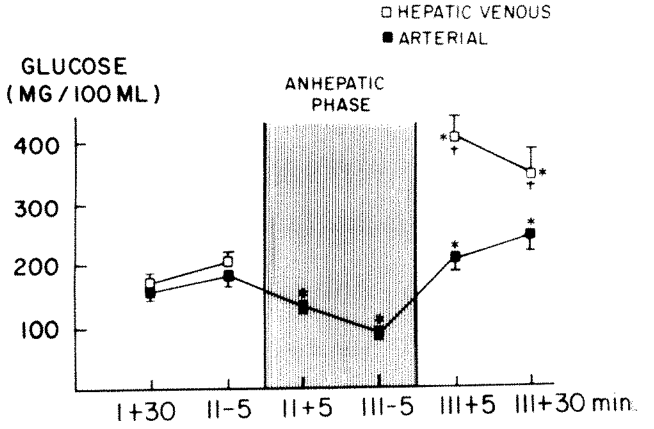

Figure 1. Blood glucose levels in arterial and hepatic venous blood during liver transplantation in 12 dogs. (Values are mean ± SEM.) (*)Different from the values in the preanhepatic stage. (+)Different from the corresponding values in arterial blood.

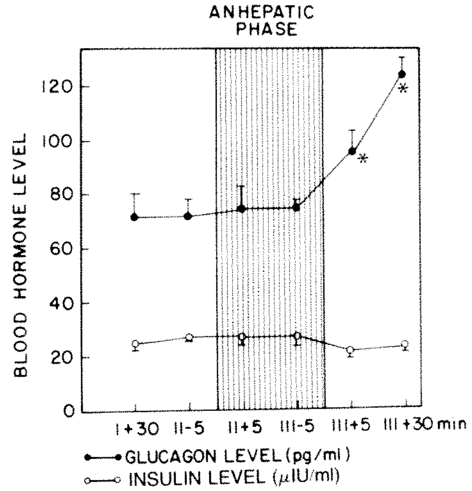

Figure 2. Arterial blood levels of glucagon and insulin during liver transplantation in five dogs. (Values are mean ± SEM.) (*)Different from the values in the preanhepatic and anhepatic stages.

Results

The preanhepatic stage lasted 78 ± 19 min, the anhepatic stage 47.5 ± 17 min, and the postanhepatic stage 92 ± 24 min. Intraoperatively, cardiovascular function was relatively stable except during the second half of the anhepatic stage and the first 15 min after reperfusion. Dopamine was infused in all animals to maintain mean arterial pressure above 70 mm Hg during the unstable period, the dose ranging from 5 to 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Laboratory data are shown in Table 1. All variables were within the normal range and stable in the preanhepatic stage. During the anhepatic stage, body temperature, hematocrit, and pH decreased. Reperfusion of the grafted liver caused a further decrease in body temperature, hematocrit, and pH. Similar changes occurred in hepatic venous blood after reperfusion, although hepatic venous blood was significantly more acidotic and had a higher potassium concentration than arterial blood.

Intraoperative blood glucose levels are presented in Figure 1. During the preanhepatic stage (stage I), arterial glucose levels were 161 ± 12 and 183 ± 16 mg/dl, and hepatic venous glucose levels were 170 ± 12 and 202 ± 15 mg/dl. The latter were slightly higher, but not significantly so. During the anhepatic stage (stage II), mean blood glucose levels decreased progressively to 135 ± 9 mg/dl after initiation of the anhepatic stage ($P < 0.05$), and to 88 ± 8 mg/dl immediately before reperfusion of the graft liver ($P < 0.05$). Blood glucose levels were between 60 and 70 mg/dl in three animals and 70 and 80 mg/dl in four animals at the end of the anhepatic stage. Blood glucose levels, increased with reperfusion of the graft liver (stage III), were significantly higher in hepatic venous blood than in arterial blood: 206 ± 17 mg/dl at III + 5 min and 240 ± 24 mg/dl at III + 30 min in arterial blood, and 405 ± 37 mg/dl at III + 5 min and 346 ± 41 mg/dl at III + 30 min in hepatic venous blood. Plasma insulin levels, initially 24.3 ± 1.0 μIU/ml, did not change significantly during the entire observation period (Fig. 2). Plasma glucagon levels did not change during the preanhepatic or anhepatic stage (71.3 ± 20.5 and 73.9 ± 27.4 pg/ml, respectively) but increased steadily after reperfusion of the graft liver, reaching peak 30 min after reperfusion (123.5 ± 33.6 pg/ml), significantly above preanhepatic and anhepatic levels. In five animals blood glucose levels were compared with the glucagon/insulin ratios, but the correlation was very poor ($r^2 = 0.02$). On completion of the study, all dogs were transfused with whole blood obtained from the organ donor dogs; ten animals received 2 units and two animals received 3 units. Two animals died of pulmonary edema and pneumothorax at the end of surgery. Three animals died postoperatively within 48 hr and seven animals lived more than 6 postoperative days.

Discussion

The liver is responsible for uptake, storage, and release of glucose, and for gluconeogenesis. The blood level of glucose is determined by the balance between release of glucose into the blood stream and glucose utilization by the body. These are influenced by, among other factors, the activities of insulin, glucagon, catecholamines, and glucocorticoids. Hepatic uptake of glucose and glycogen synthesis are enhanced by insulin. Glucagon stimulates gluconeogenesis and glycogenolysis and thereby increases hepatic output of glucose. Secretion of glucagon, epinephrine, and growth hormone can increase in response to hypoglycemia and stress. The liver is exposed to high concentrations of insulin and other hormones in portal blood, and the effects of these hormones on hepatic glucose metabolism may be more important than has been recognized. Because of the major role of the liver in glucose homeostasis, significant changes in blood glucose levels are expected during liver transplantation in experimental animals and in patients.

In the animals studied, exogenous glucose administration, including that in blood transfusions, was completely avoided. The dogs had normal preoperative hematocrits, and blood loss during surgery was minimal until the postanhepatic stage, so transfusion could be delayed until the study was completed (30 min after reperfusion). In the preanhepatic stage, glucose levels were stable, and arterial and hepatic venous blood glucose levels were similar, but initiation of venous bypass decreased hematocrit and blood glucose levels significantly. These decreases were most likely due to hemodilution from the priming solution in the bypass system, 250 ml balanced electrolyte solution. As the anhepatic stage progressed, blood glucose levels decreased further, possibly owing to continuing glucose utilization with decreased glucose production. In the present study the mean duration of the anhepatic stage was 47.5 min, about one-half the 93 min reported in clinical cases (7). With a longer anhepatic stage, glucose levels may decrease further in animals. Plasma insulin and glucagon levels did not change during the preanhepatic and anhepatic stages. Although blood glucose levels decreased during the anhepatic stage, the levels may not have been low enough to cause glucagon release.

The changes in metabolic variables with reperfusion are similar to results obtained during human liver transplantation: metabolic acidosis, hyperkalemia, hemodilution, and hypothermia caused by the release of cold, hyperkalemic, acidotic fluid from the graft liver (8–10). Reperfusion of the liver significantly increased arterial blood glucose levels. The increase may have been secondary to a massive release of glucose from the newly implanted liver, as indicated by the higher glucose level in hepatic venous blood compared with that in arterial blood and by the association of the increasing arterial glucose level with the decreasing hepatic venous glucose level. A similar observation has been made by Halliday et al., who demonstrated progressively increasing glucose levels in the hepatic venous blood of the continuously perfused pig donor liver (11). Ischemic injury in the hepatocytes may have damaged cell membrane permeability, which allowed the release of intracellular glucose (12). It is interesting to note that plasma glucagon levels progressively increased after reperfusion despite arterial hyperglycemia. The increase in glucagon levels may have been caused by delayed release of glucagon in response to a low blood sugar level during the anhepatic stage or, alternatively, the release of glucagon may have played a role in the postreperfusion arterial hyperglycemia. However, a positive relationship between blood glucose levels and glucagon/insulin ratios was not seen in this study, although the lack of correlation could be due to the small number of animals studied. The administration of dopamine could have increased the secretion of glucagon, but only minimally. Thus, sudden hyperglycemia, especially in hepatic venous blood, that occurred within 5 min after reperfusion is unlikely to be hormonal in origin. Hypothermia in the recipient dogs could have decreased glucose utilization, and the relative ischemia of the donor liver occurring after reperfusion may also have affected the graft liver's sensitivity to hormones and intracellular enzymes responsible for glycogenolysis. This study was limited to 30 min after reperfusion; glucose metabolism in the postoperative period requires further investigation. It is also unknown whether or not the amount of glucose released from the reperfused graft liver has any prognostic value with respect to functional recovery of the organ, if postreperfusion hyperglycemia were caused by ischemic damage of the donor liver.

Similar changes in glucose homeostasis are expected to be seen in patients receiving liver transplants, although there are several differences between our experimental design and clinical patient care. In the animals studied, anesthesia was maintained with ketamine, which could have increased blood glucose level indirectly by releasing catecholamines (13), and the duration of the anhepatic stage was shorter than that in patients, which might have led to the higher glucose level than the values expected in patients. However, hyperglycemia is more likely to occur in patients undergoing liver transplantation. Glucose metabolism is altered in patients with chronic liver disease, and high levels of circulating insulin are common owing to hypersecretion of insulin or inadequate hepatic clearance of insulin (14), but these patients are known to be resistant to insulin action (15). A high plasma glucagon level is frequently observed, caused by hypersecretion and the effects of portasystemic shunting (16). Clinically, glucose intolerance and higher than normal blood glucose levels are not unusual. In patients, the intraoperative transfusion of blood preserved in dextrose solution (CPDA-1), which contains 200 mg/dl of glucose, is unavoidable, and flushing of preservation solution (Collins' solution, glucose 3.75%) into the systemic circulation may supply enough glucose to maintain adequate glucose levels. The high catecholamine levels observed in patients receiving liver transplants (Uram et al., unpublished data, 1984) may counteract the peripheral effects of insulin, and possible disturbances of the hormonal balance between insulin and glucagon may occur. Furthermore, the donor organ with a longer ischemic time in patients (4–8 hr) (1) may release more glucose on reperfusion, whereas, glucose utilization is decreased by frequent inadvertent hypothermia. The effects of postreperfusion hyperglycemia on urine output and its composition were not determined in the present study. Hyperglycemia exceeding the transport maximum of the renal tubules may cause glucosuria and osmotic diuresis.

In conclusion, this study showed minimal hypoglycemia during the anhepatic stage and hyperglycemia after reperfusion of the graft liver in healthy dogs undergoing liver transplantation without exogenous glucose administration. The postreperfusion hyperglycemia appears to be secondary to a release of glucose from the newly grafted liver. The results suggest that hypoglycemia is less likely in patients when glucose is administered by transfusion of banked blood, and hyperglycemia may occur if additional exogenous glucose is given, especially after reperfusion of the graft liver.

The authors thank Marc Zapp and Frank McSteen for their technical assistance, and Lisa Cohn for her editorial help.

References

1. Starzl TE, Iwatsuki S, Van Thiel DH, et al. Evolution of liver transplantation. Hepatology 1982;2:614–636.
2. Starzl TE, Iwatsuki S, Shaw BW Jr, Gordon RD. Orthotopic liver transplantation in 1984. Transplant Proc 1985;17:250–258.
3. Aldrete JA. Liver transplantation: Intraoperative and anesthetic management. In: Arias A, Llaurado R, Nalda M, eds. Recent progress in anaesthesiology and resuscitation. Excerpta Medica: Amsterdam, 1975;387–391.
4. Tullock WC, Pinsky MR, Shaw BW, Martin DJ. Metabolic changes during the anhepatic phase of liver transplantation (Abstr). Anesthesiology 1984;61:A271.
5. Borland LM, Roule M, Cook DR. Anesthesia for pediatric orthotopic liver transplantation. Anesth Analg 1985;64:117–124.
6. Todo S, Kam I, Lynch S, Starzl TE. Animal research in liver transplantation with special reference to the dog. Semin Liver Disease 1985;4:309–317.
7. Shaw BW, Martin DJ, Marquez JM, et al. Venous bypass in clinical liver transplantation. Ann Surg 1984;200:524–534.
8. Lindop MJ, Farman JV, Smith MF. Anaesthesia: Assessment and intraoperative management. In: Calne RY, eds. Liver transplantation. Grune & Stratton: New York, 1983:121–143.
9. Martin DJ, Marquez JM, Kang YG, Shaw BW, Pinsky MR. Liver transplantation: Hemodynamic and electrolyte changes seen immediately following revascularisation (Abstr). Anesth Analg 1984;63:246.
10. Carmichael FJ, Lindop MJ, Farman JV. Anesthesia for hepatic transplantation: Cardiovascular and metabolic alterations under their management. Anesth Analg 1985:64:108–116.
11. Halliday JP, Sheil R, Hensley WJ, Bookallil J, Wotherspoon GP. Biochemical aspects of experimental hepatic allotransplantation. Arch Surg 1974;108:75–80.
12. Lambotte L, Wojcik S, Pontegnie-Istace S. Investigations on the mechanisms of action of hyperosmolar intracellular solutions used in liver preservation. In: Pegg DE, Jacobson IA, eds. Organ preservation II. Churchill Livingstone: London, 1979: 292–303.
13. Zsigmond EK, Domino EF. Clinical pharmacology and current use of ketamine. In: Aldrete JA, Stanley TH, eds. Trends in intravenous anesthesia. Year Book Medical Publishers: Chicago, 1980:283–328.
14. Collins JR, Lacy WW, Stiel JN, Crofford OB. Glucose intolerance and insulin resistance in patients with liver disease. Arch Int Med 1970;126:608–614.
15. Flier JS, Kahn CR, Roth J. Receptors, antireceptor antibodies and mechanisms of insulin resistance. N Engl J Med 1979;300:413–419.
16. Marco J, Diego J, Villanueba ML, Diaz-Fierros M, Valverde I, Segovia JM. Elevated plasma glucagon levels in cirrhosis of the liver. N Engl J Med 1973;289:1107–1111.

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1987;66:81–4

Clinical Reports

Assessment of Effect of Various Modes of Premedication on Acid Aspiration Risk Factors in Outpatient Surgery

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Stress and emotional upset increase gastric acid production and gastric volume (1,2). The presurgical period is stressful for most patients, and this may increase gastric fluid and acid production. Analyses of gastric contents after induction of anesthesia in nonobese adult outpatients undergoing elective surgery have demonstrated a significant proportion of patients to be at potential risk of acid aspiration syndrome (3,4). The effects of various types and modes of premedication (meperidine, diazepam, orally, intravenously, intramuscularly) on gastric acidity and volume are controversial (5–12). The purpose of this study was to evaluate whether or not various premedication regimens influence the risk of aspiration in outpatients undergoing elective surgery.

Methods

One hundred and twenty-five adult outpatients receiving general anesthesia for elective surgery were studied. The study was approved by the institutional review committee, and informed consent was obtained from all patients. The patients were randomly assigned into five groups of twenty-five each. Patients in group 1 received no premedication; group 2 patients received meperidine (50–100 mg) and hydroxyzine (50–100 mg) intramuscularly, whereas patients in group 3 received meperidine (25–50 mg) and prochlorperazine (2.5–5.0 mg) intravenously. Patients in group 4 received diazepam (5 mg) and prochlorperazine (2.5–5.0 mg) intravenously, and group 5 patients received diazepam (5 mg) and hydroxyzine (100 mg) by mouth. Meperidine, prochlorperazine, and diazepam were all administered slowly over a 10–15-min period in groups 3 and 4, whereas diazepam and hydroxyzine were administered to group 5 with a sip of water. All drugs were administered 45–120 min before induction of anesthesia. All patients were healthy, and none had gastrointestinal disorders.

After induction of anesthesia with thiopental, a #18 Salem sump tube was passed into the stomach and all available gastric contents were aspirated. Accurate position of the gastric tube was verified by insufflation of air through the gastric tube with simultaneous auscultation over the epigastrium. The pH was determined in the laboratory by a Corning pH meter with a silver–silver chloride combination electrode.

Patients with gastric pH ≤ 2.5 or volume ≥ 25 ml were defined as being at risk of aspiration. Risk factors were analyzed in combination and independently. One-way analyses of variance were used to compare means of the five groups. Comparisons of proportions "at risk" in the five groups were made with 5×2 χ^2 tests of independence. Differences were considered statistically significant if P values were less than 0.05.

Results

Statistical information concerning patient characteristics and fasting periods for the five groups are presented in Table 1. Sex distribution, age, height, and weight were not significantly different in the five groups. The groups did differ significantly in mean fasting time, with group 5 having a significantly longer fasting period than the other four groups, which did not differ significantly from each other.

Received from the Department of Anesthesiology, Lourdes Hospital, Paducah, Kentucky, and the Division of Statistics and Measurement, Southern Illinois University School of Medicine, Springfield, Illinois. Accepted for publication August 25, 1986.

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Table 1. Patient Characteristics and Fasting Periods

	Number of patients	Sex distribution (M/F)	Age (yr)[a]	Height (cm)[a]	Weight (kg)[a]	Fasting period (hr)[a]
Group 1: no premedication	25	11/14	33.3 ± 2.7	172.1 ± 1.6	70.8 ± 2.8	11.51 ± 0.62
Group 2: meperidine and hydroxyzine, intramuscularly	25	15/10	27.6 ± 2.2	173.3 ± 1.6	72.0 ± 3.2	11.16 ± 0.53
Group 3: meperidine and prochlorperazine, intravenously	25	14/11	31.7 ± 2.7	173.1 ± 2.1	72.6 ± 3.5	10.63 ± 0.43
Group 4: diazepam and prochlorperazine, intraveously	25	11/14	30.7 ± 2.7	171.8 ± 2.2	68.9 ± 3.7	10.60 ± 0.42
Group 5: diazepam and hydroxyzine, orally	25	12/13	33.5 ± 2.8	170.3 ± 1.4	67.9 ± 2.6	13.50 ± 0.85

[a] Values are mean ± SEM

Table 2. Gastric pH Data

	pH		Patients with pH ≤ 1.5	Patients with pH ≤ 1.8	Patients with pH ≤ 2.5
	Mean ± SEM	Range			
Group 1: no premedication	1.86 ± 0.11	1.28–3.64	5 (20%)	19 (76%)	22 (88%)
Group 2: meperidine and hydroxyzine, intramuscularly	2.10 ± 0.23	1.12–6.47	4 (16%)	16 (64%)	20 (80%)
Group 3: meperidine and prochlorperazine, intravenously	1.94 ± 0.12	1.27–4.30	5 (20%)	14 (56%)	23 (92%)
Group 4: diazepam and prochlorperazine, intravenously	1.90 ± 0.12	1.26–4.31	4 (16%)	16 (64%)	23 (92%)
Group 5: diazepam and hydroxyzine, orally	1.82 ± 0.10	1.28–2.73	4 (16%)	14 (56%)	24 (96%)

Gastric pH

The five groups did not differ significantly, either in terms of mean pH or proportion of patients with pH ≤1.5, pH ≤1.8, or pH ≤2.5. (Table 2).

Gastric Volume

The five groups did not differ significantly in terms of mean gastric volume and the proportions with volume ≥25 ml (Table 3).

Combined Risk of pH and Volume

The five groups did not differ significantly in proportion of patients with both pH ≤1.5 and volume ≥25 ml, proportion with both pH ≤1.8 and volume ≥25 ml, and proportion with both pH ≤2.5 and volume ≥25 ml (Table 3).

Discussion

Pulmonary aspiration of acidic gastric contents is a recognized hazard of anesthesia that continues to draw attention in anesthesia literature (13,14). It is generally agreed that gastric contents ≥25 ml with pH ≤2.5 are critical for the development of acid pneumonitis (15–17). However, recent evidence in experimental animals demonstrates that even patients with low volumes of gastric fluid have a high mortality if pH is very low, whereas a much higher volume than previously thought can be tolerated if the gastric fluid pH is ≥1.4 (18).

Drug absorption studies and analysis of gastric contents after induction of anesthesia in patients have shown that opioid analgesics cause delay in gastric emptying (5–7). It is also believed that anxiety and stress before surgery delay gastric emptying, in addition to increasing gastric acid production (1,2), hence

Table 3. Gastric Volume Data

	Volume (ml)					
	Mean ± SEM	Range	Patients with volume ≥ 25 ml	Patients with volume ≥ 25 ml with pH ≤ 1.5	Patients with volume ≥ 25 ml with pH ≤ 1.8	Patients with volume ≥ 25 ml with pH ≤ 2.5
Group 1: no premedication	30.0 ± 4.1	5–80	15 (60%)	5 (20%)	12 (48%)	14 (56%)
Group 2: meperidine and hydroxyzine, intramuscularly	26.2 ± 4.0	2–90	12 (48%)	3 (12%)	9 (36%)	12 (48%)
Group 3: meperidine and prochlorperazine, intravenously	25.7 ± 4.6	5–100	9 (36%)	3 (12%)	8 (32%)	9 (36%)
Group 4: diazepam and prochlorperazine, intravenously	30.0 ± 4.9	5–100	11 (44%)	4 (16%)	10 (40%)	11 (44%)
Group 5: diazepam and hydroxyzine, orally	26.0 ± 4.7	8–100	9 (36%)	2 (8%)	7 (28%)	9 (36%)

it is presumed that anxiolysis and sedation may decrease risk factors associated with gastric aspiration. However, two recent studies evaluating the effect of oral and rectal diazepam on gastric contents revealed opposing results (10,11). One study showed that orally administered diazepam reduced gastric volume and acidity, whereas the other found rectal diazepam to be ineffective in reduction of gastric acidity or volume (10,11). In the present study, patients receiving no premedication, meperidine IM or IV, diazepam IV or PO, with hydroxyzine IM or PO, or prochlorperazine IV, were comparable with respect to gastric pH and volume. The proportion of patients with gastric volume ≥25 ml was less in groups 2 to 5 receiving premedication, but the difference did not reach statistical significance. Our results demonstrated that there was neither an increase nor a decrease in gastric acidity and volume as a result of narcotic or oral premedication. In contrast to previous reports (10–12), we did not see suppression of gastric secretion by diazepam and prochlorperazine.

A pitfall in this study is the technique employed for the collection of gastric contents, as the exact location of the gastric tube at the time of aspiration of gastric juice is not known and consequently all the contents may not be obtained (3). However, any errors in estimation would be consistent across treatment groups, and comparisons of group means and proportion of patients at risk are not biased by the use of this technique.

In summary, the results of this study suggest that a significant proportion of outpatients undergoing elective surgery are at risk for aspiration pneumonitis, as 88% of unpremedicated patients have gastric pH ≤2.5, 56% have gastric contents ≥25 ml with pH ≤2.5, and significant proportions of patients also presented with pH ≤1.8 as well as pH ≤1.5. This study also demonstrated that patients receiving no premedication, meperidine IM or IV, diazepam IV or PO with hydroxyzine IM or PO, or prochlorperazine IV presented with similar gastric juice volume and pH. Thus the utilization of drugs to alter gastric contents favorably will be an adjunct to safe anesthetic practice (4,19,20).

We are grateful to the administration, outpatient surgery, operating room, and laboratory staffs for their help. We also thank Ray DeMeyer, Clyde Hadley, Martha Rust, and Stephen J. Markwell for their assistance and help.

References

1. Gray SJ, Ramsey CG. Adrenal influences upon the stomach and the gastric responses to stress. Rec Prog Horm Res 1953;13:583–617.
2. Mahl GF, Karpe R. Emotions and hydrochloric acid secretion during psychoanalytic hours. Psychosom Med 1953;15:312–26.
3. Ong B, Palahniuk RJ, Cummings M. Gastric volume and pH in outpatients. Can Anaesth Soc J 1978;25:36–9.
4. Manchikanti L, Roush JR. Effect of preanesthetic glycopyrrolate and cimetidine on gastric fluid pH and volume in outpatients. Anesth Analg 1984;63:40–6.
5. Nimmo WS, Heading RC, Wilson J, Tothill P, Prescott LF. Inhibition of gastric emptying and drug absorption by narcotic analgesics. Br J Clin Pharmacol 1975;2:509–13.
6. Nimmo WS, Heading RC, Wilson J, Prescott LF. The reversal of narcotic induced delay in gastric emptying and paracetamol absorption by naloxone. Br Med J 1979;2:1189.
7. Holdsorth JD. Relationship between stomach contents and analgesia in labour. Br Anaesth 1978;50:1145–8.
8. Gamble JA, Gaston JG, Nair SG, Dundee JW. Some pharmacological factors influencing the absorption of diazepam following oral administration. Br J Anaesth 1978;48:1181–5.
9. Todd JG, Nimmo WS. Effect of premedication on drug absorption and gastric emptying. Br J Anaesth 1983;55:1189–93.

10. Hjortso E, Mondorf T. Does oral premedication increase the risk of gastric aspiration? Acta Anaesthiol Scand 1982;26:505–6.
11. Blom H, Schmidt JF, Rytlander M. Rectal diazepam compared to intramuscular pethidine/promethazine/chlorpromazine with regard to gastric contents in pediatric anaesthesia. Acta Anaesthesiol Scand 1984;28:652–3.
12. Birnbaum D, Karmeli F, Makonnen T. The effect of diazepam on human gastric secretion. Gut 1971;12:616–20.
13. Collins VJ. Fatalities of anesthesia and surgery. JAMA 1960;172:549–55.
14. Holland R. Anesthesia related mortality in Australia. Inter Anesthesiol Clin 1984;22:61–71.
15. Mendelson CL. Aspiration of stomach contents into lungs during obstetric anesthesia. Am J Obstet Gynecol 1946;53:191–205.
16. Teabeaut JR. Aspiration of gastric contents. Am J Pathol 1952;28:51–62.
17. Roberts RB, Shirley MA. Reducing the risk of acid aspiration during Cesarean section. Anesth Analg 1974;53:859–68.
18. James CF, Modell JG, Gibbs CP, Kuck EJ, Ruiz BC. Pulmonary aspiration—effects of volume and pH in the rat. Anesth Analg 63 1984;63:665–8.
19. Manchikanti L, Colliver JA, Roush JR, Canella MG. Evaluation of ranitidine as an oral antacid in outpatient anesthesia. So Med J 1984;78:818–22.
20. Manchikanti L, Grow JB, Colliver JA, Hadley CH, Hohlbein LJ. Bicitra● (sodium citrate) and metoclopramide in outpatient anesthesia for prophylaxis against aspiration pneumonitis. Anesthesiology 1985;63:378–84.

ANESTH ANALG 85
1987;66:85–8

Intercostal Blocks with Local Infiltration Anesthesia for Extracorporeal Shock Wave Lithotripsy

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Extracorporeal shock wave lithotripsy (ESWL) is being used more frequently for disintegration of upper urinary tract stones. The procedure requires patients to be strapped in a semireclining position into an hydraulically operated chair-like support system and then submerged in water, from the clavicles down, in a large immersion tub. High-pressure shock waves are generated under water by an electrode to which 18–24 kV of energy is applied. The shock waves, transmitted through water, enter the body through the flank and are focused on the target stone using biplanar fluoroscopy. The impact of the shock waves at the entry site in the flank, the most painful stimulus in the procedure, necessitates anesthesia. To date, continuous epidural anesthesia (1) and general anesthesia with conventional mechanical ventilation or high-frequency jet ventilation have been recommended (2). Physiologic changes due to immersion, remote monitoring, and positioning present additional problems to the anesthesiologist (1,3).

In the first 800 patients treated with ESWL at the New York Hospital–Cornell Medical Center, we employed epidural, spinal, and general anesthesia with controlled ventilation. Recently, we introduced a regional anesthetic technique using intercostal nerve block combined with local infiltration, which offers a simple, safe, and acceptable method of administering anesthesia for ESWL. The following is a report of our experience with 72 patients undergoing ESWL who had intercostal nerve blocks combined with local infiltration.

Methods

Of the 342 patients undergoing ESWL at our institution between September 1985 and February 1986, 72 (21%) selected intercostal nerve block combined with local infiltration as the anesthetic technique in preference to epidural or general anesthesia. Data on these 72 patients are summarized in Table 1. The patients were brought to the anesthesia room without premedication. A peripheral intravenous catheter was inserted, and the ECG and blood pressure were monitored. Patients were placed prone with a small pillow under their heads, a soft, large pillow under the abdomen to flatten the spinal curvature in the lower back, and arms stretched above their heads. Intravenous diazepam, 10 mg (2.5–15 mg), and fentanyl, 100 μg (50–100 μg), were then administered as required, to produce sedation and analgesia prior to the block. The position of the stone was determined in relationship to the lumbar spine by review of preliminary x-rays of the kidney, ureter, and bladder (Fig. 1). The bony landmarks were used for measurements to locate the stone and, thus, the entry site of the shock wave in the flank. In the prone patient, the lumbar spinous processes were palpated, and an "X" was marked on the skin to indicate the location of the stone (Fig. 2). An approximate area of 15 × 15 cm was then marked on the flank, with "X" as its center. This area usually extended to the midline medially and to the iliac crest inferiorly. A volume of local anesthetic sufficient to infiltrate the entire area was injected subdermally in a fan-wise direction,

Table 1. Patient Data

	Mean	Range or percent
Age (yr)	46	21–74
Weight (kg)	78	45–122
Sex		
males	50	70
females	22	30
Physical Status		
ASA I	31	43
ASA II	24	33
ASA III	13	18
ASA IV	4	5

$n = 72$

Received from the Department of Anesthesiology, The New York Hospital/Cornell University Medical College, New York, New York. Accepted for publication July 23, 1986.

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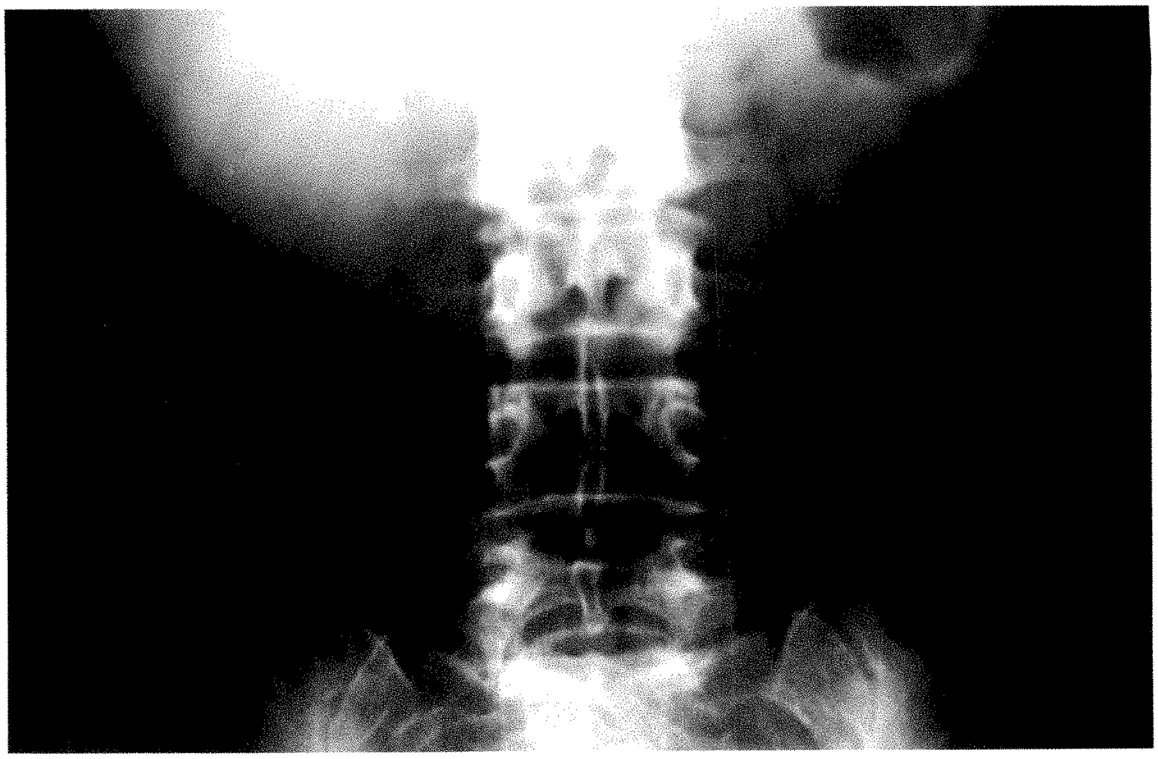

Figure 1. Position of the stone with relation to the second lumbar vertebra as seen on the pre-ESWL radiograph.

starting at the center and spanning 360°, using a 22-gauge 10-cm needle. The volume of local anesthetic (Table 2) varied with the size of the patient; however, the total dose of local anesthetic was kept below the maximum recommended dose. The last four intercostal nerves were blocked at the lower border of the corresponding ribs between the posterior axillary line and the angle of the rib as medially as possible. Local anesthetic solution (5 ml) was injected at each rib, using a 22-gauge 3.8-cm needle, after careful aspiration.

Patients were randomly given either 1% lidocaine with epinephrine for infiltration and intercostal blocks (group A, $n = 31$), or 0.25% bupivacaine for infiltration combined with a mixture of 0.5% bupivacaine and 1% lidocaine with epinephrine for the intercostal blocks (group B, $n = 41$) (Table 2). The patients were then positioned in the lithotripter support system and immersed in water up to the clavicles. During the treatment, small doses of fentanyl [average 75 μg (0–200)] were given intravenously, as required, to supplement analgesia.

Results

Patients remained hemodynamically stable, and no invasive monitoring was required. No complications related to the regional block (e.g., pneumothorax, intravascular injection) or the local anesthetics were observed.

The ESWL treatments lasted 15–85 min (average 40 min), during which an average of 1839 shocks (750–2475) was applied. The duration of fluoroscopy or the treatment was similar to that of the patients receiving general anesthesia for ESWL [average immersion time 40 min (15–70)]. All procedures were completed satisfactorily, and the urologists rated the operating conditions as "excellent." The majority of the patients were comfortable while immersed during the procedure and often fell asleep. Occasional sensations were reported by the patients as mild "slaps" or "thumps," or moderate "gas pain around the umbilicus." In all instances, intravenous supplementation relieved the symptoms. Sedation was mild, however, and patients were easily arousable and able to communicate with the physicians during the treatment.

At the end of the procedure, all but four patients were awake and coherent. They were discharged directly to their rooms. Four patients were sent to the recovery room for an average of 60 min (50–75 min). The average duration from the time a patient was brought to the ESWL unit to discharge from the ESWL unit was 93 min (60–165), which included waiting time in the anesthesia room, the time required for the

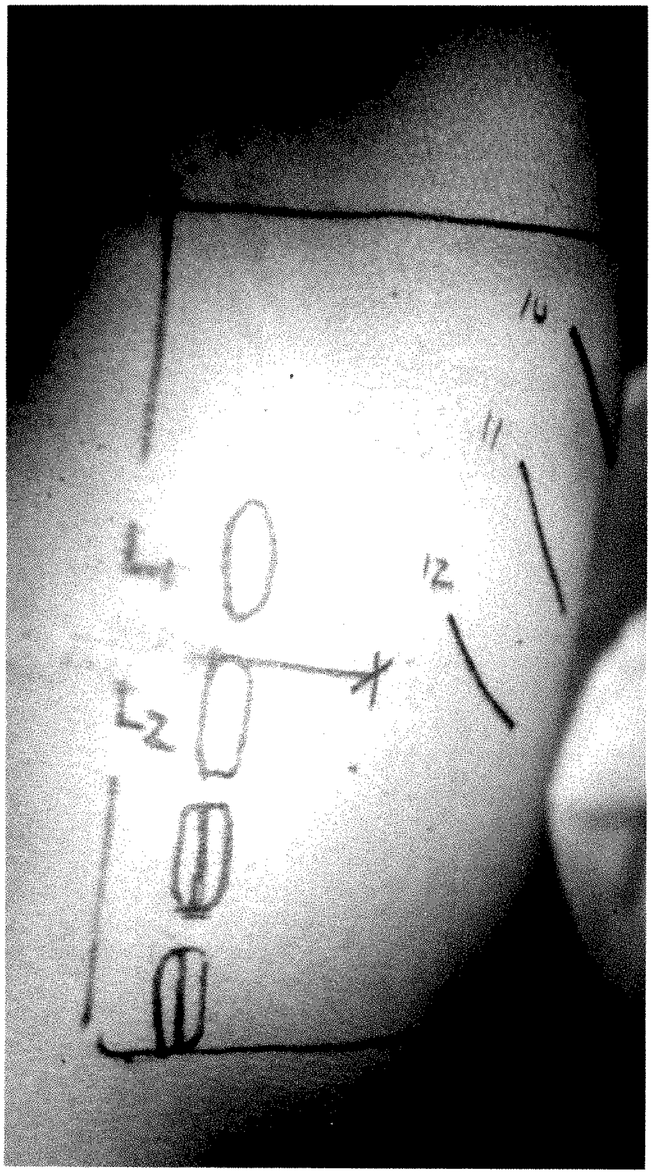

Figure 2. Shock wave entry site with surface marking of the ribs and lumbar spinous processes. "X" location of the stone based on the radiograph.

block (average 10 min), and procedures like cystoscopy and insertion of ureteral stents. In many cases, the block was administered to one patient in the anesthesia room while another was being treated in the tub. The patients rated their anesthetic experience as "highly acceptable" and indicated that they would choose the same anesthetic should retreatment be necessary. Four patients who required retreatment did choose this anesthetic technique again.

In the postoperative period, over 70% of the patients required no pain medication. Narcotic analgesics were required for postoperative pain related to the movement of stone fragments. The patients described the feeling at the shock entry site as "mild soreness" in the flank that did not require medication. Postoperative narcotic requirement was similar in both groups (Table 2).

Discussion

In the German experience, local infiltration, sedation, or both, proved inadequate in providing anesthesia for ESWL (personal communication, Werner C. Weber, Munich, Germany). We found the addition of intercostal blocks to local infiltration improved the quality of anesthetic. The impact of the shock wave, felt over a wide area in the flank, has been described as a sharp, stinging pain at the skin combined with deep somatic (subcutaneous, muscular) and visceral pressure discomfort. The intercostal block has been helpful by blocking the deep somatic sensation. The block has been most beneficial when performed at the angle of the rib. In the very obese, or in patients where the bony landmarks were not clearly palpable, we elected to perform the blocks more laterally at a point where the ribs were palpable, to reduce the risk of complications. The visceral sensation, however, was not blocked, and patients had mild to moderate discomfort, which was relieved by intravenous medication.

The technique has been well accepted by both patients and urologists. Patient movement during treatment has not been a problem. The treatment time, fluoroscopy time, and the number of shock waves required were similar in patients receiving regional block, epidural, or general anesthesia. In fact, at times the patients have been able to help the urologist localize the stone by deep breathing or breathholding on request.

This technique offers several advantages when compared with epidural or general anesthesia. It eliminates the arduous task of lifting and positioning anesthetized patients in the gantry chair, and also protects the patient from injury due to positioning. None of the patients in this group developed hypotension during the procedure. In our experience, the incidence of relative hypotension (mean arterial pressure less than 80% of preanesthetic levels) in patients undergoing ESWL has been 18% with epidural and 13% with general anesthesia. Absence of motor blockade, which accompanies epidural anesthesia, has been a definite advantage with this technique, allowing direct discharge of the patient to his room, rapid recovery, and early ambulation. Extracorporal shock wave lithotripsy patients often require pretreatment cystoscopy to insert a ureteral stent. This anesthetic technique,

Table 2. Comparison of Local Anesthetics Used and Postoperative Narcotic Requirement

Group	Procedure	Local anesthetic (c̄ epinephrine 1:200,000)	Average volume (ml) (range)	Postoperative narcotics required (%) 0–6 hr	Postoperative narcotics required (%) 0–24 hr
A (*n* = 31)	Infiltration	1% Lidocaine	36 (20–60)	23	29
	Intercostal block	1% Lidocaine	20	—	—
B (*n* = 41)	Infiltration	0.25% Bupivacaine	42 (20–60)	26	29
	Intercostal block	0.5% Bupivacaine with 1% lidocaine	20	—	—

combined with sedation, has offered effective analgesia for both cystoscopy and ESWL, without the dangers of transporting an anesthetized, intubated patient between the cystoscopy and ESWL areas. Furthermore, the unpleasant side effects of general anesthesia (nausea, vomiting, hangover) have been avoided. We have not noticed any advantage in using a longer acting anesthetic (like bupivacaine) as compared with lidocaine, in obtaining postoperative pain relief.

In summary, intercostal blocks combined with local infiltration is a simple and inexpensive anesthetic technique for ESWL, which obviates the complexities of epidural anesthesia, general anesthesia, high frequency jet ventilation, and invasive monitoring. We have found it to be safe, effective, and well accepted in the 72 patients we have treated.

References

1. Duvall JO, Griffith DP. Epidural anesthesia for extracorporeal shock wave lithotripsy. Anesth Analg 1985;64:544–6.
2. Esch JS, Kochs E, Meyer WH. Improved efficiency of extracorporeal shock wave lithotripsy during high frequency jet ventilation. Anesthesiology 1985;63:A177.
3. Carlson CA, Gravenstein JS, Banner MJ, Boysen PG. Monitoring techniques during anesthesia and HFJV for extra-corporeal shock wave lithotripsy. Anesthesiology 1985;63:A178.

ANESTH ANALG
1987;66:89–90

Atlantoaxial Subluxation with Symptomatic Spinal Cord Compression in a Child with Down's Syndrome

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Common physical findings in patients with Down's syndrome include generalized hypotonia and laxity of joint ligaments (1–3). Under general anesthesia, meticulous attention in positioning these children is necessary to avoid hyperextension injury of peripheral nerves. Ligamentous laxity of the atlantoaxial joint may allow subluxation (C1–2) that can lead to cervical spinal cord compression (2,4). This is a report of a child with Down's syndrome who suffered progressive symptoms of cervical spinal cord compression after cardiac surgery.

Case Report

A 4.5-year-old, 14.1-kg, 89-cm boy with mosaic trisomy 21 was admitted for correction of a ventricular septal defect. During the 4 months prior to admission, the patient's exercise tolerance had worsened with increased fatiguability and decreased ambulation. Prior to surgery, the child was able to walk in an upright position without support, and had attained the developmental milestones of a 3-year-old.

On physical examination the blood pressure was 104/60 mm Hg, and the pulse was regular at 108 beats/min. A 4/6 systolic ejection murmur with a +2/+4 thrill was heard at the left sternal border. Mild scoliosis with splinting to the right was noted. The child's ventricular septal defect ($\dot{Q}_P:\dot{Q}_S$ of 2.8:1 and pulmonary artery pressure of 55/20 mm Hg) was closed during an unremarkable anesthetic and surgical procedure. Anesthesia had been induced inhalationally by mask using a 50:50% mixture of nitrous oxide: oxygen and a slowly increasing concentration of halothane up to 2%. After paralysis with 0.14 mg/kg pancuronium, the child was intubated without special cervical protection. The patient was extubated 2 hr after arrival in the intensive care unit, and his postoperative course was unremarkable except for the development of postpericardiectomy syndrome, which was treated effectively with aspirin. However, the patient's locomotion changed from walking upright to crawling on all fours. In spite of the physical findings of bilateral extensor plantar reflexes and diffuse hypotonia of the lower extremities, the patient was discharged from the hospital.

At the first postoperative follow-up visit, the patient was found to be growing and physically developing well, though he continued to crawl on all fours, rather than walking upright. Physical examination revealed paraparesis and increased deep tendon reflexes in the lower extremities, as well as ankle clonus and extensor plantar reflexes. Combined myelography and computerized tomography of the upper cervical spine revealed the body of the second cervical vertebrae and the base of the odontoid process were posteriorly subluxed, causing narrowing of the spinal canal between the base of the odontoid process and the dorsal arch of the first cervical vertebra. The cervical spinal cord was slightly flattened at that level. The patient underwent surgical fusion of the upper cervical spine without incident. Currently (8 months after cervical fusion), the patient has regained a normal gait pattern and ambulatory abilities.

Discussion

Recent recommendations by the American Academy of Pediatric's Committee on Sports Medicine have drawn attention to the potential risk of spinal cord injury for children with Down's syndrome (4). Due to ligamentous laxity and cervical vertebral abnormalities, some 20% of children with Down's syndrome develop atlantoaxial subluxation (3,5,6), pre-

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Received from the Departments of Anesthesiology and Cardiothoracic Surgery, Deborah Heart and Lung Center, Browns Mills, New Jersey, the Department of Anesthesiology, University of Pennsylvania, Philadelphia, and the Department of Pediatrics, College of Physicians and Surgeons of Columbia University, New York, NY. Accepted for publication July 28, 1986.

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disposing them to cervical spinal cord compression. The diagnosis of atlantoaxial subluxation can be made with lateral extension and flexion roentgenograms of the upper cervical spine. An odontoid process (axis) to anterior arch (atlas) distance of greater than 4.5 mm indicates abnormal instability and subluxation of the junction (4,7). Children with atlantoaxial subluxation are at risk for cervical spinal cord injury during hyperextension, hyperflexion, or increased rotation of the neck.

Signs of cervical spinal cord compression include a mixture of upper and lower motor neuron defects. One of the earliest signs is loss of ambulatory skills (2), evidenced by a broad-based gait, clumsiness, and increased fatigue on walking (4). Other common signs include spasticity and hyperreflexia of the lower extremities, extensor plantar reflexes, loss of bowel and bladder control, and neck posturing (torticollis). Early diagnosis allows surgical intervention to prevent progressive nerve injury.

Because spontaneous subluxation of the atlantoaxial junction can produce spinal cord compression, preoperative evaluation by the anesthesiologist should be directed toward discovery of any preexisting signs or symptoms of cervical cord compression. A high degree of suspicion is necessary because subtle symptoms may be attributed to other disease processes. In the present case, the increased fatiguability on walking and decrease in ambulation were thought to indicate progression of the cardiac disease without due consideration given to the possibility of cervical spinal cord compression. Evaluating these symptoms in children with Down's syndrome is also more difficult due to the marked delays that may occur in motor and developmental milestones. Eliciting a history of regression from previously attained skills in ambulation or toilet training are important clues. In our case, the immediate postoperative loss of upright locomotion was ignored due to a lack of suspicion for subluxation in spite of the presence of positive physical findings. Luckily, irreversible damage to the spinal cord did not occur. If a child has symptoms potentially referable to cervical cord compression, lateral cervical films should be performed to discover whether the child has subluxation (4). If subluxation exists, further evaluation with computerized tomography and myelography is indicated.

Most children with Down's syndrome coming to the anesthesiologist's attention have neither lateral neck films nor symptoms attributable to cervical cord compression. Because the risk of atlantoaxial subluxation is so great in this group, special neck protection is necessary. The first step in avoiding accidental subluxation is the education of all medical personnel concerning the increased risks of patients with Down's syndrome for cervical subluxation. Education of the operating room, recovery room, and intensive care unit personnel is of particular importance because they will be providing care when the child is in a sedated or paralyzed condition. High-risk perioperative periods for extension–flexion as well as rotational cervical stress include laryngoscopy and tracheal intubation, positioning, transport, tracheal suctioning, and roentgenogram plate placements. Meticulous attention in supporting the head and neck during these critical periods should be provided. Of particular importance to the anesthesiologist is avoidance of hyperextension during tracheal intubation.

In summary, 20% of children with Down's syndrome have subluxation of their atlantoaxial (C1–2) junction, predisposing them to cervical spinal cord injury. Special care is necessary to prevent neurological complications by protecting the cervical spine during the anesthetic, especially at the times of tracheal intubation, patient positioning and transport.

References

1. Rabe EF. The hypotonic infant. J Pediatr 1964;64:422–40.
2. Hreidarsson S, Magram G, Singer H. Symptomatic atlantoaxial dislocation in Down syndrome. Pediatrics 1982;69:568–71.
3. Semine AA, Ertel AN, Goldberg MJ, Bull MJ. Cervical-spine instability in children with Down syndrome (trisomy 21). J Bone Joint Surg 1978;60-A:649–52.
4. Committee on sports medicine. Atlantoaxial instability in Down syndrome. Pediatrics 1984;74:152–4.
5. Tishler J, Martel W. Dislocation of the atlas in mongolism. Radiology 1965;84:904–6.
6. Martel W, Tishler JM. Observations on the spine in mongoloidism. AJR 1966;97:630–8.
7. Locke GR, Gardner JI, Van Epps EF. Atlas-dens interval (ADI) in children. AJR 1966;97:135–40.

ANESTH ANALG
1987;66:91–3

Probable Seizures after Sufentanil

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Use of the newer potent synthetic narcotic agonists has flourished due to their inherent ability to provide analgesia and anesthesia while preserving hemodynamic stability. Both high- and low-dose regimens using fentanyl and, more recently, sufentanil are in wide clinical use.

Reported adverse effects of fentanyl include intraoperative awareness, chest wall rigidity during induction, and, rarely, generalized seizures after use of either high- or low-dosage regimens (1,2). In theory, similar disadvantages might be expected to exist with sufentanil, a more potent narcotic congener of the parent molecule.

To date, however, there has been no mention in the literature of convulsive reactions associated with sufentanil. We report two recent cases in which generalized or focal seizure-like activity occurred after administration of small doses of sufentanil.

Case Reports

Case 1

A 79-year-old, 50-kg woman was admitted with obstructive jaundice. Past medical history was remarkable only for mild Parkinson's disease. She was taking no medications. She was scheduled for cholecystectomy, choledochojejunostomy, and gastrojejunostomy after medical evaluation demonstrated a mass at the head of the pancreas without evidence of metastasis. All laboratory tests, with the exception of alkaline phosphatase 380 U/L, SGOT 95 U/L, and SGPT 86 U/L, were within normal limits.

After atropine, 0.4 mg intramuscularly (IM), anesthetic induction began with the patient breathing 100% oxygen. Sufentanil, 0.04 mg, was given intravenously (IV). When she became drowsy, though still conscious, an additional 0.02 mg was injected. Loss of lid reflex occurred 2 min later. Blood pressure and pulse were 130/85 mm Hg and 66 beats/min, respectively, as ventilation was then controlled. Hypoxia was not evident. Generalized tonic–clonic movements of the arms and legs started 30 sec later. Upward deviation of the eyes simultaneously occurred. These movements abruptly ceased 0.5 min after thiopental, 50 mg, was administered IV. Subsequently tracheal intubation was performed with the aid of succinylcholine 50 mg IV. An arterial blood sample was drawn as the thiopental was injected. The plasma sufentanil concentration, determined by radioimmunoassay, was 1.07 ng/ml (3). We decided to continue surgery because she was otherwise stable. There were no problems intraoperatively and no postoperative neurologic sequelae.

Case 2

A 67-yr-old, 66-kg man was scheduled for elective cholecystectomy for cholelithiasis and splenectomy for hypersplenism. Past history was pertinent for Waldenstrom's macroglobulinemia. Additionally, the history was significant for symptomatic gastroesophageal reflux and stable ischemic heart disease. There was no history of myocardial infarction, but typical anginal symptoms were precipitated by moderate reductions in serum hemoglobin concentration.

There were no symptoms of hyperviscosity syndrome. At the time of surgery the serum viscosity was normal. No coagulopathy was evident, and there was no antecedent history of change in mentation, transient ischemic attacks, or focal/generalized seizure disorder. Chronic medications included ranitidine 150 mg and metoclopramide 10 mg, both twice a day.

Preoperative medication included meperidine, 50 mg, hydroxyzine, 25 mg, and glycopyrrolate, 0.2 mg, all given IM 1 hr before surgery. A "modified" rapid sequence induction utilizing sufentanil was chosen to

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Received from the Department of Anesthesiology, Monmouth Medical Center, Long Branch, New Jersey. Accepted for publication July 14, 1986.

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blunt the hemodynamic effects of laryngoscopy and tracheal intubation. The patient was preoxygenated for 3 min before sufentanil in 0.01-mg increments to a total of 0.04 mg was administered over 5 min. Pancuronium, 1 mg IV was given for defasciculation. Before apnea or loss of consciousness, the sudden onset of left upper extremity tonic–clonic movements, upward deviation of the eyes with subsequent vertical nystagmus, and unresponsiveness occurred. Cricoid pressure was applied. Thiopental, 175 mg IV, and succinylcholine, 100 mg IV, were administered to stop the seizure activity and facilitate intubation. Blood pressure, heart rate, and ECG remained stable. An arterial blood sample drawn 5 min after intubation and initiation of controlled ventilation (Vt = 700 ml, f = 8/min, $F_{I_{O_2}}$ = 1.0) had a pH of 7.41, a P_{CO_2} of 37 mm Hg, and a P_{O_2} of 223 mm Hg.

Anesthesia was subsequently maintained with N_2O 50% and O_2, isoflurane, and pancuronium for muscle relaxation. The intraoperative and postoperative periods were uneventful. Neurological examination on emergence, and serially postoperatively, was normal. There were no neurological sequelae.

Discussion

It is speculative whether or not the tonic–clonic movements described above in our patients, or by others, were true seizures, because EEG documentation was not available (1,2). Somatic muscle rigidity has been offered to explain these phenomena because studies using large doses of fentanyl failed to reveal EEG activation. The successful use of small doses of nondepolarizing muscle relaxants to control such "seizures" has lead to the conclusion that these phenomena, indeed, represent "muscle rigidity" (4–6). In our patients, a small dose of thiopental eliminated the reaction in the first case. Larger doses have been given successfully to relax a "board-like abdomen" associated with morphine in a prior study (7).

Sufentanil, recently introduced into clinical practice, depresses the cortex in rats and humans (8,9). However, there is evidence that subcortical neuroexcitation with cortical depression may also occur in rats (9). Seizures, for example, were documented by EEG in rats after sufentanil administration. Additionally, regional increases in cerebral glucose utilization in certain limbic structures (amygdala, caudate, and ventral thalamic nuclei) were noted (9). It is possible that similar effects might not be demonstrable in humans because routine scalp EEG electrode monitoring does not detect subcortical seizure activity (10). Until sophisticated EEG monitoring is performed in humans, assigning an etiology to the changes we observed in these two patients (e.g., neuroexcitation vs muscular rigidity) would be premature.

An interesting common feature in the two cases described is their potential deficiency in central nervous system dopamine. Patients with Parkinson's disease have deficient dopamine neurotransmitter; rigidity is a common symptom. Metoclopramide, which was used in our second patient, inhibits cerebral dopamine. Although rigidity has not been described with its use, other extrapyramidal signs, such as torticollis, trismus, and akathasia have been reported (11,12).

Regardless of the etiology, tonic–clonic movements induced by sufentanil should be treated immediately so an airway can be secured and ventilation controlled to prevent hypoxemia and hypercarbia. It seems prudent to administer small amounts of thiopental empirically; it will depress the cortex, lessen the chance of awareness, and possibly stop the muscle movements. Succinylcholine should be given to facilitate intubation and ventilation. It may be safe to continue with the planned surgical procedure in cases such as ours in which the abnormal neurological response was transient, and because there were no postoperative neurological sequelae.

Because small doses of sufentanil have elicited this reaction, perhaps all patients given sufentanil should be preoxygenated prior to induction. Although premedication with diazepam or barbiturates increase the threshold for seizures, it is unknown whether they will prevent these tonic–clonic movements.

In summary, two cases are presented in which suspected seizure activity occurred during anesthetic induction after administration of small doses of sufentanil. In both instances "seizures" were abrupt in onset, and unrelated to antecedent clinical signs of hypoxia or significant change in vital signs. Symptoms were rapidly ablated by intravenous administration of thiopental. The etiology of the observed abnormalities is as yet unclear. The role, if any, of deficient CNS dopamine stores awaits clarification. Additionally, further studies to investigate the potential importance of subcortical neuroexcitation appear warranted.

The authors thank Dr. Edward D. Miller JR for his review of the manuscript.

References

1. Rao TLK, Mummaneni N, El-Etr AA. Convulsions: an unusual response to intravenous fentanyl administration. Anesth Analg 1982;61:1020–1.
2. Sebel AM, Bovill JG. Fentanyl and convulsions. Anesth Analg 1983;62:858–9.
3. Michiels M, Hendriks R, Heykants J. Radioimmunoassay of

the new opiate analgesics alfentanil and sufentanil. Preliminary pharmacokinetic profile in man. J Pharm Pharmacol 1983;35:86–93.

4. Safat AM, Daniel D. Grand mal seizures after fentanyl administration. Anesthesiology 1983;59:78.
5. Benthuysen JL, Stanley TH. Concerning the possible nature of reported fentanyl seizures. Anesthesiology 1985;62:205.
6. Murkin JM, Moldenhauer CC, Hug CC Jr, Epstein CM. Absence of seizures during induction of anesthesia with high-dose fentanyl. Anesth Analg 1984;63:489–94.
7. Freund FG, Martin WE, Wong KC, Hornbein TF. Abdominal-muscle rigidity induced by morphine and nitrous oxide. Anesthesiology 1973;38:358–62.
8. Fahmy NR. Sufentanil: a review. In: Estefanous FG, ed. Opioids in anesthesia. Boston: Butterworth, 1984:132–8.
9. Young ML, Smith DS, Greenberg J, Relvich M, Harp JR. Effects of sufentanil on regional cerebral glucose utilization in rats. Anesthesiology 1984;61:564–8.
10. Bickford RG. Activation procedures and special electrodes. In: Klass DW, Daly DD, eds. Current practice of clinical electroencephalography. New York: Raven Press, 1979:269–305.
11. Pinder RM, Brogden RN, Sawyer RR, Speight TM, Avery GS. Metoclopramide. A review of its pharmacologic properties and clinical use. Drugs 1976;12:81–131.
12. Kris MG, Tyson LB, Gralla RJ, Clark RA, Allen JC, Reilly LK. Extrapyramidal reactions with high-dose metoclopramide. NEJM 1983;309:433–4.

ANESTH ANALG
1987;66:94–6

Changes in Anterior Fontanel Pressure during Cardiopulmonary Bypass and Hypothermic Circulatory Arrest in Infants

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Profound hypothermic circulatory arrest (HCA) is a widely used technique in infant cardiac surgery. The hemodynamic, metabolic, and catecholamine changes associated with HCA have been reported (1–3), as have both early and late neurologic sequelae (4,5). Changes in cerebral hemodynamics and intracranial pressure (ICP) associated with HCA have not been reported.

The Ladd monitor (Ladd Research Industries, Inc., Burlington, VT) of anterior fontanel pressure (AFP) is a noninvasive indicator of ICP. This pressure transducer was designed for ICP monitoring and utilizes a fiberoptic sensor and a pneumatic tube and bellows operating on the applanation principle. The principle and the monitor have been previously described (6–8), and acceptable accuracy has been demonstrated (6,9,10).

Because the understanding and prevention of undesirable neurologic sequelae associated with HCA (4,5) requires documentation of the many variables contributing to cerebral hemodynamics, we used the Ladd monitor to record changes in AFP during cardiopulmonary bypass (CPB) and HCA in 10 infants.

Methods

This study was approved by the institutional review board of The Children's Hospital in Denver. The ten infants studied underwent repair of a variety of congenital cardiac defects. Their ages ranged from 1 day to 23 weeks (mean 10.4 weeks) and their weights from 2.7 to 6.7 kg (mean 4.3 kg).

They were anesthetized with fentanyl 30–60 μg/kg and isoflurane 0.5%. Pancuronium was used for muscle relaxation. Phenytoin 7 mg/kg and methylprednisolone 30 mg/kg were administered intravenously to all patients prior to CPB. After anesthetic induction, ice bags were applied to the head to facilitate brain cooling and were left in place until rewarming CPB.

After induction of anesthesia, tracheal intubation, and insertion of vascular catheters, the head was supported in a neutral position by a foam ring. The anterior fontanel was shaved, and tincture of benzoin was applied to the surrounding scalp. Because application force of the Ladd sensor can affect the accuracy of its measurements (11,12), we used the application technique described by Hill and Volpe (10). This technique, using adhesive foam to secure the sensor to the anterior fontanel, is both accurate and reliable (10). We used the Ladd 10004 sensor and the Ladd M1000 pressure monitor.

Mean arterial pressure (MAP) was directly monitored via radial or brachial artery catheters using Bentley Trantec transducers (Irvine, CA) and a Hewlett-Packard monitor (Waltham, MA). MAP and AFP were recorded on a Ladd recorder. Nasopharyngeal and rectal temperatures were monitored.

The surgeon cannulated the ascending aorta and inserted a single right atrial cannula for venous return. CPB was instituted using a pulsatile flow pump oxygenator/heat exchanger (Cobe-Stockert, Cobe Laboratories, Lakewood, CO), and core cooling began immediately. When nasopharyngeal and rectal temperatures of 14–18°C were attained, perfusion was stopped and the intracardiac repair was performed during total circulatory arrest of 12–57 min.

After repair of the defect, perfusion was resumed and the patient rewarmed. All patients received an infusion of sodium nitroprusside 2–4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during warming CPB. When temperature was 37°C and hemodynamic stability was present, CPB was discontinued. All patients were given calcium chloride 10–20 mg/kg at this point. After cessation of CPB, three patients required infusion of dopamine 5–15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and two required isoproterenol 0.1–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. AFP monitoring was discontinued 30 min after cessation of CPB. Cerebral perfusion pressure (CPP) was estimated using the formula CPP = MAP − AFP.

Statistical analysis of the data was performed using

Received from the Departments of Anesthesiology and Perinatology, The Children's Hospital, Denver, Colorado. Accepted for publication August 18, 1986.

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Table 1. Pressure Changes During Cardiopulmonary Bypass and Circulatory Arrest

	Pre-CPB (baseline)	Cooling CPB	Circulatory arrest	Warming CPB peak	Warming CPB	Post-CPB
Duration (min)	—	10.3 ± 2.3	41.5 ± 14.1	3.6 ± 1.5	31.2 ± 15.3	—
AFP (mm Hg)	6.3 ± 2.6	5.9 ± 3.3	2.9 ± 1.3[a]	10.7 ± 4.9[a]	4.9 ± 1.5	5.3 ± 2.5
MAP (mm Hg)	53 ± 9	44 ± 7[a]	6 ± 5[a]	60 ± 10	47 ± 9	55 ± 8
CPP (mm Hg)	47 ± 11	36 ± 7[a]	3 ± 4[a]	49 ± 12	42 ± 10	50 ± 10
$P\text{CO}_2$ (mm Hg)	34 ± 8	34 ± 5	—	—	29 ± 5	32 ± 3

Values are means ± SD; $n = 10$.
Abbreviations: CPB, cardiopulmonary bypass; AFP, anterior fontanel pressure; MAP, mean arterial pressure; CPP, estimated cerebral perfusion pressure.
[a] Significantly different from control ($P < 0.05$).

repeated measures analysis of variance and the paired *t*-test. A correlation coefficient was calculated to determine the correlation of AFP change with duration of HCA. Statistical significance was assumed when $P < 0.05$.

Results

The results are summarized in Table 1 and depicted in Figure 1. A significant ($P < 0.01$) decrease in AFP occurred at the time of circulatory arrest in all patients. Immediately upon initiation of warming CPB after HCA, AFP increased to a level significantly ($P < 0.05$) above baseline (prior to cooling CPB). This increase was transient in all patients, lasting from 2 to 6 min (mean 3.6 min). AFP then decreased to a level not different from baseline for the duration of the study. The amount of increase in AFP did not correlate with duration of HCA.

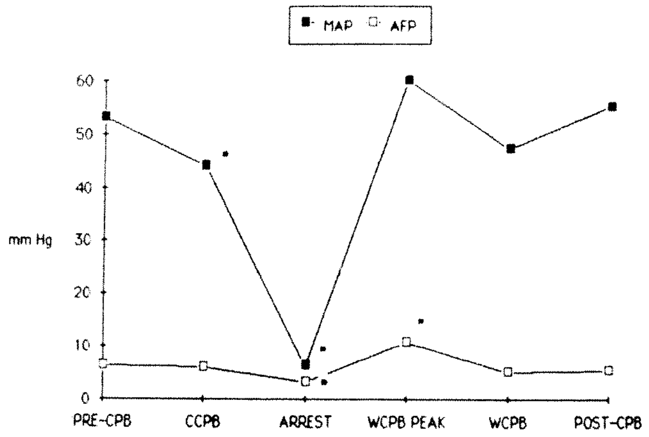

Figure 1. Changes in anterior fontanel pressure and mean arterial pressure in infants undergoing cooling cardiopulmonary bypass (CCPB), hypothermic circulatory arrest, and warming cardiopulmonary bypass (WCPB). Asterisk denotes values significantly different ($P < 0.05$) from control (pre-CPB).

Discussion

This study demonstrates a consistent, transient, statistically significant increase in AFP during the first few minutes of warming CPB after HCA. MAP increased slightly during this time, but not significantly above baseline levels.

Other physiologic changes associated with HCA may help explain the increase in AFP. Johnston et al. (2), observed hypercarbia and respiratory acidosis during the first 5 min of initial reperfusion after HCA, but not later during warming CPB. Blood pressure (1) and plasma catecholamine levels (3) are transiently elevated during initial warming CPB. Cerebral blood flow (CBF) is increased by hypercarbia (13), and autoregulation of CBF is impaired by acidosis and hypoxia (14). It is possible, therefore, that autoregulation of CBF, impaired during HCA, becomes reestablished only after several minutes of warming CPB, thus allowing AFP to increase "unregulated" with MAP and CBF during initial reperfusion. Because hypothermia alone is associated with reductions in CBF (15,16) and ICP (17) and an increase in cerebral vascular resistance (15), further data during profound hypothermia and HCA will be necessary to elucidate the mechanism of AFP increase that we observed.

The anesthetic drugs administered to our patients probably did not significantly affect AFP during the study. Isoflurane causes a dose-related increase in ICP during normocarbia (18,19) but not during hypocarbia (18). Our patients received low-dose isoflurane during mild to moderate hypocarbia (Table 1). Fentanyl transiently decreases CBF (20), maintains cerebral vascular responsivity (21), and probably has little effect on ICP.

Phenytoin and methylprednisolone were given to our patients prior to cooling CPB. Phenytoin decreases cerebral metabolic rate and increases CBF (22). Another corticosteroid, dexamethasone, decreases brain edema in neurosurgical patients (23). We do not know whether these drugs affected AFP during this study.

Nitroprusside infusion via the internal jugular vein was started at the onset of warming CPB. It is conceivable that this drug contributed to the short duration of increased AFP. Because of the catheter deadspace and the extracorporeal circuit volume, we expect that the effects of nitroprusside would not be observed for several minutes. Although the cerebral vasculature may already have been dilated by the hypercarbia and hypoxia associated with HCA (2,13,14), systemic vasodilation by nitroprusside, occurring after a few minutes of reperfusion, could have increased the capacity of the systemic vasculature to accept the rise in blood volume, thus lowering cerebral blood volume and pressure.

Infusions of dopamine or isoproterenol, when indicated, were not started until late in warming CPB; thus they did not affect the observed AFP changes.

If observed changes in AFP were found to be deleterious to the patient, it may be possible to pharmacologically prevent AFP increases with barbiturates (13). Such treatment might, however, be accompanied by undesirable impairment of myocardial function.

Although there are potential deleterious effects of a significant AFP increase, we are not able to conclude that the observed AFP changes are of clinical importance. The increase of AFP during initial reperfusion after HCA could cause a reduction in CPP if MAP decreased. This did not happen in our patients, in whom MAP and, thus, estimated CPP were insignificantly above control levels (Table 1).

Postoperative neurologic impairment was not observed in our patients. A long-term study has shown a correlation between impairment of intelligence and duration of HCA (5), but the AFP changes were similar in all of our patients, regardless of HCA duration.

Finally, the highest mean AFP, 10.7 mm Hg, although significantly above control levels in our patients, is still within the range of normal AFP in unanesthetized neonates reported by other investigators using the Ladd monitor (6–8).

We conclude that a transient increase in AFP occurs during the initial reperfusion of CPB after HCA in infants. Although the increase was of statistical significance, it is probably of minimal clinical significance. The peak AFP levels were modest, and impairment of CPP or postoperative neurologic function was not demonstrated. Studies of CBF associated with HCA may elucidate the mechanism, and further studies of neurologic sequelae may determine its clinical importance.

References

1. Barratt-Boyes B. Profound hypothermia—technical aspects. Singapore Med J 1973;14:445–7.
2. Johnston AE, Radde IC, Steward DJ, Taylor J. Acid–base and electrolyte changes in infants undergoing profound hypothermia for surgical correction of congenital heart defects. Can Anaesth Soc J 1974;21:23–45.
3. Turley K, Roizen M, Vlahakes GJ, Graham B, Ebert PA. Catecholamine response to deep hypothermia and total circulatory arrest in the infant lamb. Circulation 1980;62:I175–9.
4. Belsey RHR, Dowlatshahi K, Keen G, Skinner DB. Profound hypothermia in cardiac surgery. J Thorac Cardiovasc Surg 1968;56:497–509.
5. Wells FC, Coghill S, Caplan HL, Lincoln C, Kirklin JW. Duration of circulatory arrest does influence the psychological development of children after cardiac operation in early life. J Thorac Cardiovasc Surg 1983;86:823–31.
6. Vidyasagar D, Raju TNK. A simple noninvasive technique of measuring intracranial pressure in the newborn. Pediatrics 1977;59:957–61.
7. Raju TNK, Vidyasagar D. Intracranial and cerebral perfusion pressure: methodology and clinical considerations. Med Instrum 1982;16:154–6.
8. Philip AGS, Long JG, Donn SM. Intracranial pressure. Sequential measurements in full-term and preterm infants. Am J Dis Child 1981;135:521–4.
9. Myerberg DZ, York C, Chaplin ER, Gregory GA. Comparison of noninvasive and direct measurements of intracranial pressure. Pediatrics 1980;65:473–6.
10. Hill A, Volpe JJ. Measurement of intracranial pressure using the Ladd intracranial pressure monitor. J Pediatr 1981;98:974–6.
11. Horbar JD, Yaeger S, Philip AGS, Lucey JF. Effect of application force on noninvasive measurements of intracranial pressure. Pediatrics 1980;66:455–7.
12. Walsh P, Logan WJ. Continuous and intermittent measurement of intracranial pressure by Ladd monitor. J Pediatr 1983;102:439–42.
13. Smith AL, Wollman H. Cerebral blood flow and metabolism: effects of anesthetic drugs and techniques. Anesthesiology 1972;36:378–400.
14. Ong BY, Greengrass R, Bose D, Gregory G, Palahniuk RJ. Acidemia impairs autoregulation of cerebral blood flow in newborn lambs. Can Anaesth Soc J 1986;33:5–9.
15. Michenfelder JD, Theye RA. Hypothermia: effect on canine brain and whole-body metabolism. Anesthesiology 1968; 29:1107–12.
16. Govier AV, Reves JG, McKay RD, Karp RB, Zorn GL, Morawetz RB, Smith LR, Adams M, Freeman AM. Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. Ann Thorac Surg 1984;38:592–600.
17. Rosomoff HL, Gilbert R. Brain volume and cerebrospinal fluid pressure during hypothermia. Am J Physiol 1955;183:19–25.
18. Adams RW, Cucchiara RF, Gronert GA, Messick JM, Michenfelder JD. Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. Anesthesiology 1981;54:97–9.
19. Todd MM, Drummond JC. A comparison of the cerebrovascular and metabolic effects of halothane and isoflurane in the cat. Anesthesiology 1984;60:276–82.
20. Michenfelder JD, Theye RA. Effects of fentanyl, droperidol, and Innovar on canine cerebral metabolism and blood flow. Br J Anaesth 1971;43:630–6.
21. McPherson RW, Traystman RJ. Fentanyl and cerebral vascular responsivity in dogs. Anesthesiology 1984;60:180–6.
22. Cullen JP, Aldrete JA, Jankovsky L, Romo-Salas F. Protective action of phenytoin in cerebral ischemia. Anesth Analg 1979;58:165–9.
23. Maxwell RE, Long DM, French LA. The clinical effects of a synthetic gluco-corticoid used for brain edema in the practice of neurosurgery. In: Reulen HJ, Schurmann K, eds. Steroids and brain edema. Heidelberg: Springer-Verlag, 1972:219–32.

Letters to the Editor

Morphine Antagonism with Nalbuphine

To the Editor:

The recent paper by Bailey et al. (1) provides timely insight into the resurgent use of mixed agonist–antagonist opioids to reverse opioid-induced respiratory depression. However, to fully understand the study, one must reexamine the nature of the interaction between the pure opioid agonists and the mixed compounds first noted three decades ago with nalorphine and morphine (2) and elucidated more fully a decade later (3).

The net effect of an agonist–antagonist opioid in a patient given a pure opioid agonist depends on how depressed the patient is to begin with. The interaction with a pure opioid agonist converges to a point that corresponds to the limited maximum effect or "ceiling" of the agonist–antagonist. If the existing effects of the agonist opioid at the time the agonist–antagonist opioid is given greatly exceed this ceiling effect, the agonist–antagonist will reverse the agonist by substituting its limited respiratory depression, analgesia, and sedation for the more marked effects of the agonist. If, as in the study of Bailey et al. (1), the agonist effect approximates the ceiling effect of the agonist–antagonist, little or no change will be noted after administration of the agonist–antagonist. In keeping with this, in the study by Bailey et al. nalbuphine had little or no effect on the existing morphine effect. The prolonged respiratory depression noted after nalbuphine administration was essentially the effect of the agonist–antagonist, because the morphine action had already begun to decrease as indicated by data following placebo "reversal" with saline.

The authors appropriately suggest that a larger dose of morphine, such as 0.4 mg/kg, would have been more likely to demonstrate a reversal effect with nalbuphine. They state that nalbuphine may not be reliable in reversing lesser analgesic doses of morphine. It would appear more correct to state that nalbuphine is inappropriate in such cases because it has a similar magnitude of effect.

Clinical observations after pure opioid agonist anesthesia confirm the efficacy of nalbuphine in reversing severe respiratory depression (4). Such studies also suggest that reversal of sufficient duration to prevent significant renarcotization requires a dose of nalbuphine that produces the drug's maximal or ceiling effect (i.e., about 0.2 mg/kg). The effects of such nalbuphine doses are emphasized by the data of Bailey (1) and others (5–7). Therefore, one should not expect to find a completely awake normocapneic patient.

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References

1. Bailey PL, Clark NJ, Pace NL, Isern M, Stanley TH. Failure of nalbuphine to antagonize morphine: a double-blind comparison with naloxone. Anesth Analg 1986;65:605–11.
2. Lasagna L, Beecher HK. The analgesic effectiveness of nalorphine and nalorphine-morphine combinations in man. J Pharmacol Exp Ther 1954;112:356–63.
3. Belleville JW, Fleischli G. The interaction of morphine and nalorphine on respiration. Clin Pharmacol Ther 1968;9:152–61.
4. Moldenhauer CC, Roach GW, Finlayson DC, et al. Nalbuphine antagonism of ventilatory depression following high dose fentanyl anesthesia. Anesthesiology 1985;62:647–50.
5. Romagnoli A, Keats AS. Ceiling effect for respiratory depression by nalbuphine. Clin Pharmacol Ther 1980;27:478–85.
6. Julien RM. Effects of nalbuphine on normal and oxymorphone-depressed ventilatory responses to carbon dioxide challenge. Anesthesiology 1982;57:A320.
7. Gal TJ, DiFazio CA, Moscicki J. Analgesic and respiratory depressant activity of nalbuphine: a comparison with morphine. Anesthesiology 1982;57:367–74.

Hazards of Amnesia after Midazolam in Ambulatory Surgical Patients

To the Editor:

Since its recent release, midazolam has become popular as an intravenous premedicant for ambulatory surgical patients. This popularity is due to the drug's lack of pain on injection or phlebitis and the excellent sedation provided (1,2). However, several ambulatory patients have complained that they do not remember meeting their surgeon or anesthesiologist before the operation, and query whether they were indeed present. Further investigation revealed that these patients had received midazolam, 2 mg IV, in the preoperative waiting area. We caution against the administration of midazolam until after all significant personnel have identified themselves to the patient and all questions have been answered.

There is also the potential hazard of amnesia for postoperative instructions, although this has not occurred in our experience. The duration of amnesia after 5 mg midazolam has been reported as 20–60 or more minutes (3,4),

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which encompasses the recovery period for several ambulatory procedures. It is important that all patients who have had ambulatory anesthesia or sedation receive written as well as verbal discharge instructions, particularly if these patients have been given even modest doses of midazolam.

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References

1. Philip BK. Supplemental medication for ambulatory procedures under regional anesthesia. Anesth Analg 1985;64:1117–25.
2. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. Anesthesiology 1985;62:310–24.
3. Connor JT, Katz RL, Pagano RR, Graham GW. RO 21-3981 for intravenous surgical premedication and induction of anesthesia. Anesth Analg 1978;57:1–5.
4. Dundee JW, Wilson DB. Amnesic action of midazolam. Anaesthesia 1980;35:459–61.

Three Components of Anesthesia: One More Reason to Accept the Concept

To the Editor:

Dr. Pinsker presented the concept that paralysis (absence of movement or skeletal muscle tone in the operative field), unconsciousness, and attenuation of stress response (heart rate, blood pressure) are the three necessary and sufficient components of anesthesia (1). His concept has important differences from the concept of four components of anesthesia suggested by Woodbridge: sensory block, motor block, block of reflexes, and mental block (2). The basic differences consist of exclusion of analgesia (sensory block) as a component of anesthesia in Pinsker's concept and substitution of Woodbridge's block of reflexes by a similar notion of attenuation of stress response. The viability of this approach is shown by the mere fact that another similar concept was presented 30 years after Woodbridge's attempt to divide anesthesia into components and achieve them using different means.

We would like to present an additional reason to accept the concept of three components of anesthesia. The reason is based on the fact that interactions of various drugs used to provide anesthesia can be different for different components of anesthesia. For example, it was found that fentanyl–thiopental interaction results in antagonism for blockade of purposeful movement response to noxious stimulation (paralysis according to Pinsker's terminology) and at the same time in synergism in relation to the hypnotic effect (unconsciousness) (3). Morphine and halothane interact to provide summation in relation to the blockade of purposeful movement to noxious stimulation (paralysis) and antagonism in relation to attenuation of heart rate response to the same stressful stimulation (stress response) (4). Reserpine enhances the hypnotic effect of fentanyl (unconsciousness) and antagonizes its effect on the motor response to noxious stimulation (paralysis) (5). In our opinion, it is quite difficult, or perhaps impossible, to study the interactions of anesthetic agents without analyzing their combined effects on each of the components of anesthesia separately.

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References

1. Pinsker MC. Anesthesia: a pragmatic construct (Letter). Anesth Analg 1986;65:819–20.
2. Woodbridge PD. Changing concepts concerning depth of anesthesia. Anesthesiology 1957;18:536–50.
3. Kissin I, Mason JO III, Bradley EL Jr. Morphine and fentanyl interactions with thiopental. 14th Int'l Congress of Israel Soc Anesthesiol, Haifa, 1986.
4. Kissin I, Kerr CR, Smith LR. Morphine-halothane interaction in rats. Anesthesiology 1984;60:553–61.
5. Kissin I, Brown PT. Reserpine-induced changes in anesthetic action of fentanyl. Anesthesiology 1985;62:597–600.

Avoidance of Recall during General Anesthesia for Cesarean Section

To the Editor:

The comparison by Schultetus et al. of ketamine and thiopental induction for cesarean section identified ketamine's advantage in contributing to amnesia (1). Concerning neonatal impact, methohexital (Brevital) apparently offers no further advantage (2).

But what about those first 10 minutes of anesthesia, until delivery, that was associated with an eight per cent incidence of recall in Schultetus's patients (1)? An induction drug plus 70% nitrous oxide (1) need not be the limits of obstetrical general anesthesia prior to delivery. One-half MAC of a halogenated anesthetic combined with 70% N_2O will insure amnesia (3), preserve uterine tone (4), yet avoid neonatal depression (5).

The continued judicious use of volatile anesthetics (5) can obviate the problem of awareness addressed by Schultetus et al. (1) by providing patients with a complete anesthetic.

Daniel B. Gould, MD
Creve Coeur, MO 63141

References

1. Schultetus RR, Hill CR, Dharamraj CM, Banner TE, Berman LS. Wakefulness during cesarean section after anesthetic induction with ketamine, thiopental, or ketamine and thiopental combined. Anesth Analg 1986;65:723–8.
2. Morgan M, Holdcroft A, Whitwam JG. Comparison of thiopentone and methohexitone as induction agents for cesarean section. Anaesth Intens Care 1980;8:431–5.
3. Stoelting RK, Longnecker DE, Eger EI. Minimum alveolar concentrations in man on awakening from methoxyfluorance, halothane, ether and fluroxene anesthesia; MAC awake. Anesthesiology 1970;33:5–9.
4. Marx GF, Kim YI, Lin CC. Postpartum uterine pressures under halothane and enflurane anesthesia. Obstet Gynecol 1978;51:695–8.
5. Shnider SM, Levinson G. Anesthesia for cesarean section. In: Shnider SM, Levinson G, eds. Anesthesia for obstetrics. Baltimore: Williams and Wilkins, 1979:261–7.

Book Reviews

Drug Therapy During Pregnancy

T.K.A.B. Eskes and M. Finster, eds. London:
Butterworths, 1985, 230 pp, $85.00.

Currently there is great interest in the fetal and neonatal effects of drugs used during pregnancy. This is reflected by the recent introduction of *Drug Therapy During Pregnancy*, a 12-chapter, multiauthored text edited by two noted perinatal pharmacologists. Recognizing that antepartum and/or intrapartum maternal drug therapy is often necessary, this book reviews not only the fetal and neonatal effects of maternally administered drugs, but also the indications, efficaciousness, and pharmacokinetics of a wide variety of drugs used during pregnancy. As stated in the preface, the editors hope that the provision of this information will "enable the practitioner to make rational decisions in terms of risk to benefit ratio as far as both the mother and the fetus are concerned."

The first three chapters of the book are general in nature and discuss current trends in the use of drug therapeutics during pregnancy, the pharmacokinetics of the maternal-fetal unit, and the pathogenesis of congenital malformations. The next seven chapters review and summarize the literature regarding the clinical use and the fetal/neonatal effects of specific classes of pharmacologic agents administered during pregnancy: antihypertensives, nonsteroidal antiinflammatory agents, anticonvulsants, hormonal therapy, anesthetics, oxytocic agents, and β-adrenergic agonists. The final two chapters discuss drug-induced fetal heart rate changes and teratogenic/carcinogenic toxicology.

Although this reviewer finds the book's British style of in-text referencing to be quite distracting, the text has, to its credit, very few typographical and spelling errors. Furthermore, despite its small size, the book covers an extensive variety of drugs, with cardiac glycosides, tricyclic antidepressants, and anticoagulants the only omissions.

As in any multiauthored text, certain chapters seem stronger than others. This reviewer found the chapters on anticonvulsants, hormonal therapy, and anesthetics to be particularly well-written and informative. Examples of weakness include the chapters on antihypertensives and drug-induced changes in fetal heart rate. The former cites extremely outdated references to support the claim that ganglionic blockers should not be used during pregnancy. In addition, this chapter fails to mention the use of nitroglycerin as an antihypertensive drug. The chapter on fetal heart rate changes repeatedly cites statistical analyses of drug-induced changes in both the long-term irregularity index and the interval difference index, two indices of fetal heart rate variability. However, nowhere in the chapter is there any indication of either how these indices are measured and calculated, or even the units in which they are expressed.

The obstetric anesthesiologist and the practicing obstetrician will find this book to be a good resource for information regarding the clinical treatment of problems requiring pharmacologic therapy during pregnancy and as a reference source for drug-induced fetal and neonatal effects. The practicing clinical anesthesiologist who spends the majority of his or her time outside of the obstetric suite, however, will find very little in this book that he or she will use in the day-to-day practice of anesthesia.

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Patient-Controlled Analgesia

M. Harmer, M. Rosen, and M.D. Vickers, eds. London:
Blackwell Scientific Publications, 1985, 199 pp, $30.25.

This book is a compilation of papers presented at the proceedings of the First International Workshop on Patient Controlled Analgesia (PCA) held in the UK in 1984. It consists of 11 chapters divided into four sections with a total of 199 printed pages interspersed with numerous graphs, figures, and tables. There are also two color plates illustrating seven PCA models now available in the USA and Europe. The list of authors is impressive and represents the researchers, clinicians, and members of PCA industry from both sides of the Atlantic. The sections are divided appropriately to present research into analgesic drugs, basic concepts of PCA equipment development, clinical PCA regimens, and future roles of PCA. A foreword written by E.M. Papper rationalizes the need for concepts of PCA and how it differs from previous thrusts of developing new analgesic drugs for providing adequate postoperative pain relief. The editors hope that this book will be of interest to those al-

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ready using PCA methods and will answer many of the questions posed by clinicians. The chapters are concise and written by established authorities on PCA. Each chapter illustrates a certain point but is not complete by itself.

Section 1 describes the terminology used in patient controlled analgesia, the pharmacokinetics of opioid analgesics with special reference to PCA, patient characteristics influencing pain relief, and clinical traits of analgesic drugs. In Section 2, the authors explore the theoretical and practical requirements for PCA systems. In Section 3, comparisons are made of PCA with alternative techniques, practical experience obtained for postop pain via PCA for obstetrics, terminal cancer, and use of PCA for epidural opiate administration. In Section 4, the authors summarize their impressions of the cost, patient selection, methods of delivery, choice of agent, patient safety, efficacy of PCA, and its future role in clinical practice.

Some of the chapters are of poor quality and do not have enough depth; however, this is to be expected from publications converted from papers presented at proceedings. This reviewer was particularly impressed with the material presented in the following chapters: Chapter 2, pharmacokinetics of opioid analgesics; and Chapter 5, modeling, estimation, and control for demand analgesia. They are well-written and concise, and they provide easy to understand diagrams and tables. Most of the other chapters are easy to understand but do have a drawback of being very short.

This monograph has achieved what it had set to do, i.e., describe the state of the art of PCA and answer the commonly asked questions about its techniques. However, if the same authors had set out to write a book rather than compile presentations of the proceedings, they would have produced a better product. Because PCA technique is increasingly being used in clinical practice today, I do congratulate the editors and the publisher for their foresight in bringing the much needed updated material on the subject.

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Erratum

Azad SS, Maguire D, Goldberg ME. Junctional Rhythm Can Mimic Air Embolism during Precordial Doppler Monitoring. Volume 65, Number 10, October 1986.

Page 1084:

The authors wish to inform readers that Figures 1 and 2 were inadvertently mislabeled. Thus the figure legends should be reversed.

A Guide for Authors

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Nicholas M. Greene, MD
Editor in Chief
Anesthesia and Analgesia
Yale University School of Medicine
333 Cedar Street, New Haven, CT 06510

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The submitted manuscript should be accompanied by a covering letter that must include a statement to the editor about all submissions and previous reports that might be regarded as prior or duplicate publication of the same, or very similar, work. The title page and abstract of such material should be included with the submitted manuscript to help the editor decide how to deal with the matter.

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *Annals of Internal Medicine* 1982;96:766–71 and *Lancet* 1982;284:1766–70.

No manuscripts describing investigations carried out in humans will be accepted for publication unless the text states that the study was approved by the authors' institutional human investigation committee and that written informed consent was obtained from all subjects or, in minors, by parents. No manuscript describing investigations in animals will be accepted for publication unless the text states that the study was approved by the authors' institutional animal investigation committee.

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☐ Original articles describe in 3000 words or less clinical or laboratory investigations.

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2. *Personal author(s) books and monographs*
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3. *Chapter in a book*
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2. O'Connor M, Woodford FP. Writing scientific papers in English: an ELSE-Ciba Foundation guide for authors. Amsterdam: Elsevier-Excerpta Medica, 1975.

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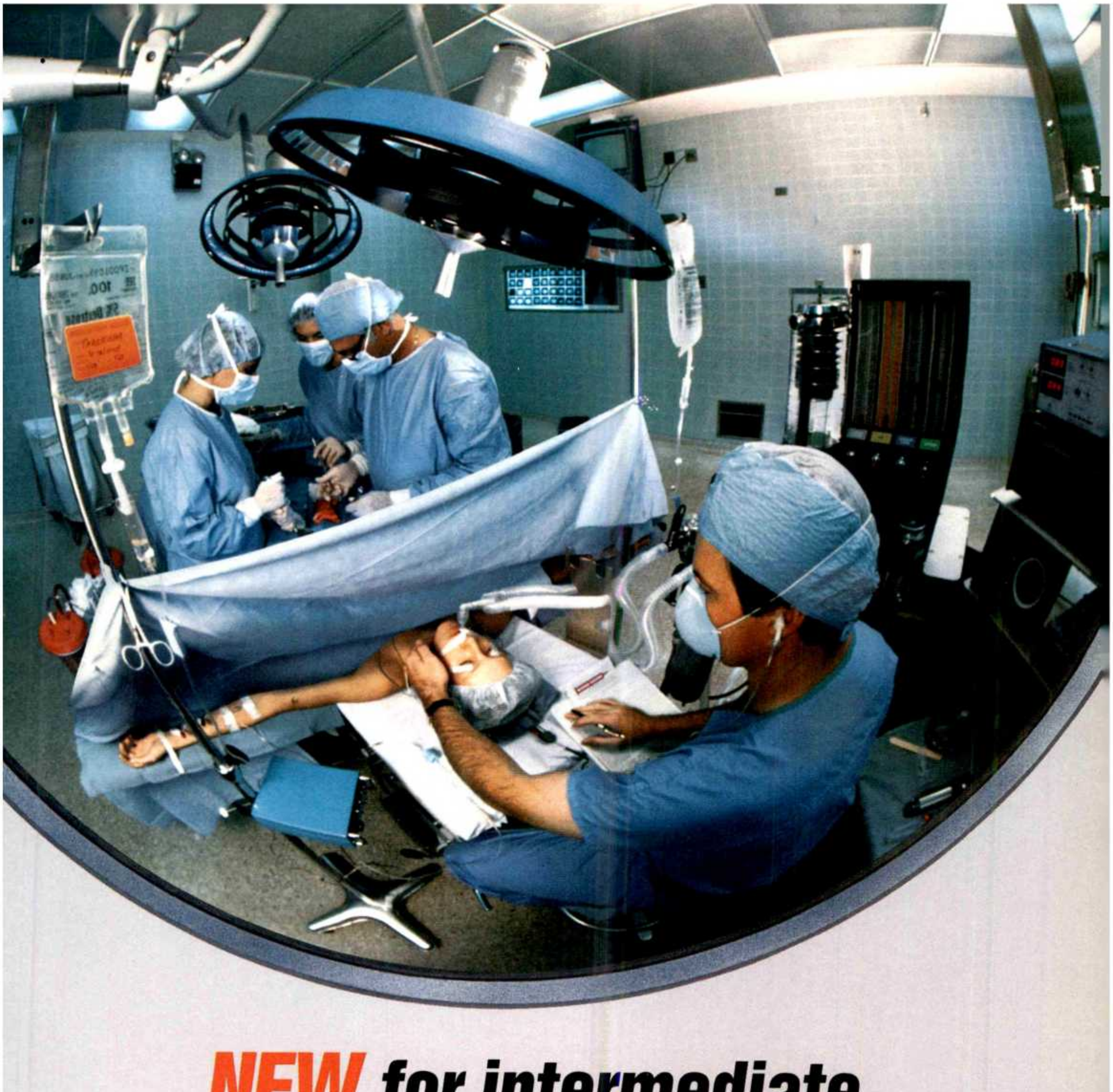

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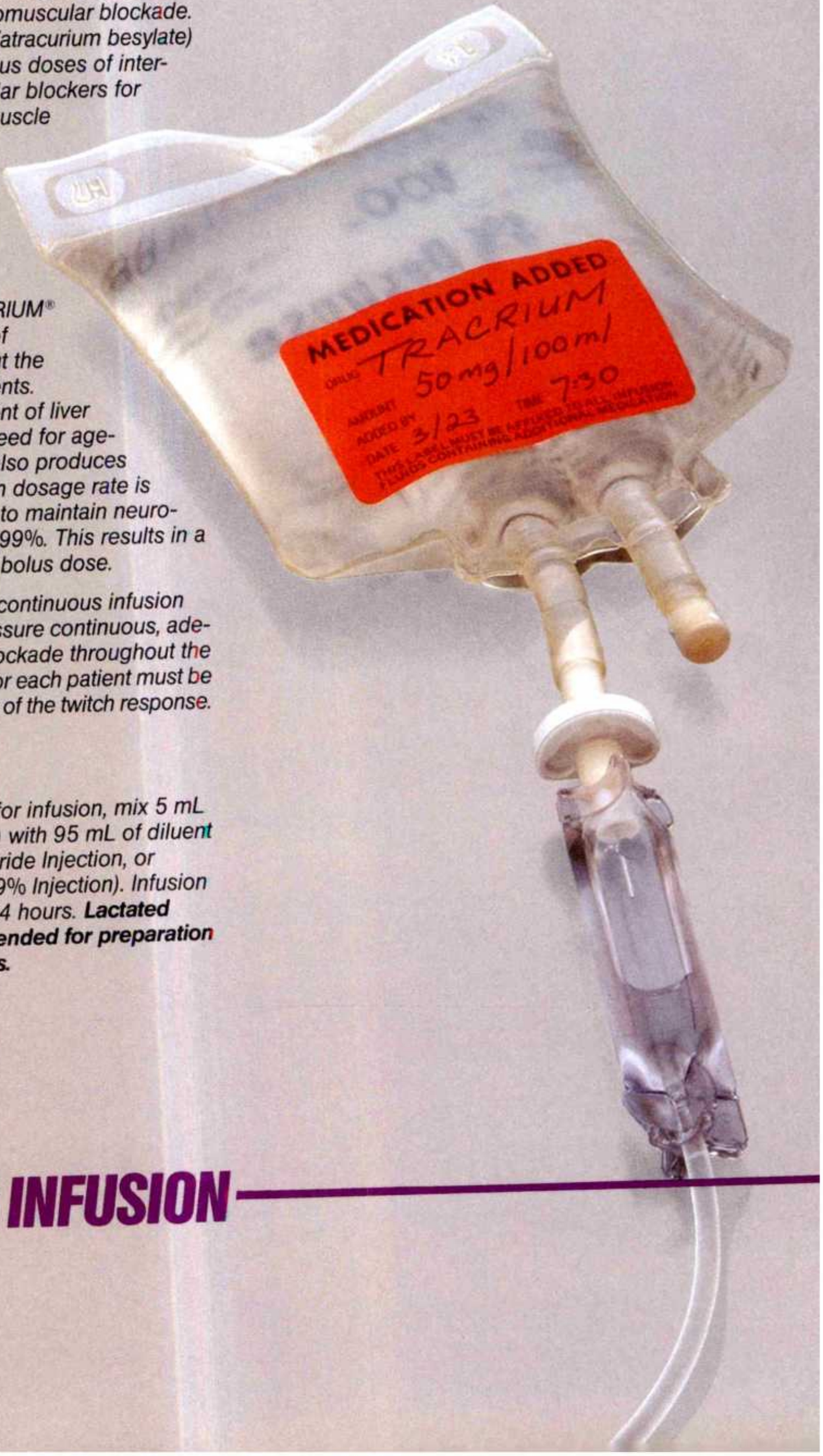
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Initial infusion dose: *Infuse TRACRIUM® at a rate of 9-10 µg/kg/min to maintain 89-99% neuromuscular blockade until steady-state relaxation is achieved. Dosage should be titrated to the individual patient's needs.*

Maintenance infusion dose: *Once steady-state neuromuscular blockade is achieved, an infusion rate of 5-9 µg/kg/min is adequate to maintain continuous blockade in the 89-99% range for most patients under balanced anesthesia. Occasional patients may require as little as 2 µg/kg/min, or as much as 15 µg/kg/min for maintenance.*

Dose Calculations:

TRACRIUM INFUSION DELIVERY RATE µg/kg/min	**INFUSION DELIVERY RATE 0.5 mg/mL SOLUTION mL/kg/min**	**mL/kg/hr**
5	0.010	0.60
6	0.012	0.72
7	0.014	0.84
8	0.016	0.96
9	0.018	1.08
10	0.020	1.20

Maintenance infusion rates should be reduced by approximately one-third in the presence of steady-state enflurane or isoflurane; smaller reductions are required for halothane. Hypothermia (25°C-28°C) can prolong the effect of surgical relaxation, so infusion rate should be reduced by about one-half during the hypothermic period.

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TRACRIUM® INJECTION
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Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:

General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether the drug is excreted in human milk.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS:

Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients with 0% change in heart rate. At doses of ≥0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate.

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequent reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Bolus Doses for Intubation and Maintenance of Neuromuscular Blockade:

Adults: A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically required neuromuscular blockade generally lasts 20 to 35 minutes under balanced anesthesia. Under balanced anesthesia, recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg, to adjust for the potentiating effects of these anesthetic agents. With halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria.

Children and Infants: No Tracrium dosage adjustments are required for pediatric patients two years of age or older. A Tracrium dose of 0.3 to 0.4 mg/kg is recommended as the initial dose for infants (1 month to 2 years of age) under halothane anesthesia. Maintenance doses may be required with slightly greater frequency in infants and children than in adults.

Special Considerations: An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for adults, children, or infants with significant cardiovascular disease and for adults, children, or infants with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated. There has been no clinical experience with Tracrium in these patients, and no specific dosage adjustments can be recommended. No Tracrium dosage adjustments are required for patients with renal disease.

Use by Infusion: After administration of a recommended initial bolus dose of Tracrium (0.3 to 0.5 mg/kg), a diluted solution of Tracrium can be administered by continuous infusion to adults and children aged 2 or more years for maintenance of neuromuscular blockade during extended surgical procedures. Infusion of Tracrium should be individualized for each patient. The rate of administration should be adjusted according to the patient's response as determined by peripheral nerve stimulation.

Infusion of Tracrium should be initiated only after early evidence of spontaneous recovery from the bolus dose. An initial infusion rate of 9 to 10 μg/kg/min may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 5 to 9 μg/kg/min should be adequate to maintain continuous neuromuscular blockade in the range of 89 to 99% in most pediatric and adult patients under balanced anesthesia.

The neuromuscular blocking effect of Tracrium administered by infusion is potentiated by enflurane or isoflurane and, to a lesser extent, by halothane. Reduction in the infusion rate of Tracrium should, therefore, be considered for patients receiving inhalation anesthesia. The rate of Tracrium infusion should be reduced by approximately one-third in the presence of steady-state enflurane or isoflurane anesthesia; smaller reductions should be considered in the presence of halothane. In patients undergoing cardiopulmonary bypass with induced hypothermia, the rate of infusion of Tracrium required to maintain adequate surgical relaxation during hypothermia (25° to 28°C) has been shown to be approximately half the rate required during normothermia.

Spontaneous recovery from neuromuscular blockade following discontinuation of Tracrium infusion may be expected to proceed at a rate comparable to that following administration of a single bolus dose.

Tracrium infusion solutions may be prepared by admixing Tracrium Injection with an appropriate diluent such as 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, or 5% Dextrose and 0.9% Sodium Chloride Injection USP. Infusion solutions should be used within 24 hours of preparation. Spontaneous degradation of Tracrium has been demonstrated to occur more rapidly in lactated Ringer's solution than in 0.9% sodium chloride solution. Therefore, it is recommended that Lactated Ringer's Injection USP not be used as a diluent in preparing solutions of Tracrium for infusion.

The amount of infusion solution required per minute will depend upon the concentration of Tracrium in the infusion solution and the dose of Tracrium desired (see table).

Tracrium (atracurium besylate)—Rates of Infusion for Concentrations of 0.2 and 0.5 mg/ml

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (ml/kg/min)	
	0.2 mg/ml*	0.5 mg/ml**
5	0.025	0.010
6	0.030	0.012
7	0.035	0.014
8	0.040	0.016
9	0.045	0.018
10	0.050	0.020

*2 ml of 1% (10 mg/ml) Tracrium Injection added to 98 ml of diluent

**5 ml of 1% (10 mg/ml) Tracrium Injection added to 95 ml of diluent

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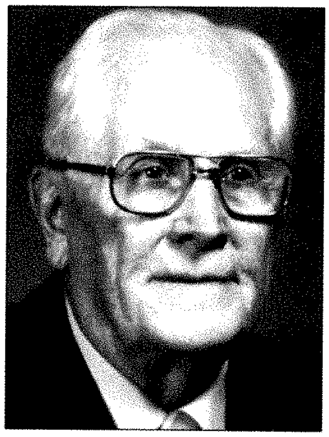
John W. Severinghaus, MD, FFARCS
Professor of Anesthesia
University of California Medical Center
San Francisco, California

When the American Society of Anesthesiologists recently named Dr. Severinghaus to receive its first "Excellence in Research" Award, it recognized not only his pioneering efforts in developng oxygen and carbon dioxide electrodes, but also his important work on the uptake of anesthetic gases in humans and his role in the development of the MAC concept. In accepting our invitation to present the fifth T.H. Seldon Distinguished Lecture, he joins his illustrious predecessors – Doctors H.J.C. Swan, Edmond I. Eger II, M.T. "Pepper" Jenkins, and J. Alfred Lee – in doing honor not only to Dr. Seldon and the IARS, but to the specialty as well.



T.H. Seldon, MD, FFARCS (I)

Dr. Seldon continues to actively enjoy his retirement years in Minnesota and Arizona and looks forward to hearing Dr. Severinghaus' presentation in Florida. The IARS is again pleased to honor him for his 23-year tenure as Editor of *Anesthesia and Analgesia*, from 1954 to 1976.

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Secretary
American Board of Anesthesiology
100 Constitution Plaza
Hartford, Connecticut 06103.

The deadline for receipt of completed applications in the Board office has been extended to June 10, 1987.

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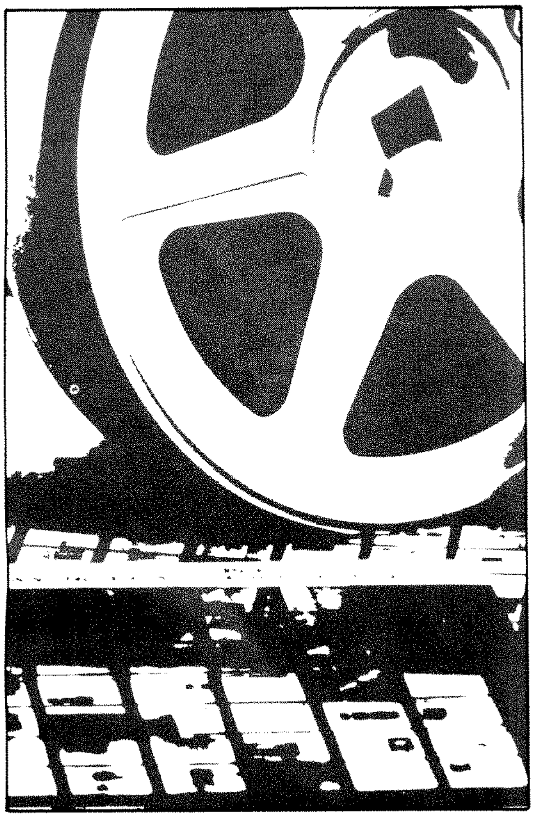

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INDICATIONS—Pyridostigmine bromide is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

CONTRAINDICATIONS—Known hypersensitivity to anticholinesterase agents; intestinal and urinary obstructions of mechanical type.

WARNINGS—Pyridostigmine bromide should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants, prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in an occasional patient, atropine and anti-shock medication should always be readily available.

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

Use in Pregnancy—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

ADVERSE REACTIONS—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

DOSAGE AND ADMINISTRATION—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Reversal dosages range from 0.1-0.25 mg./kg. Usually 10 or 20 mg. of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

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1. Gyermek L: Clinical studies on the reversal of the neuromuscular blockade produced by pancuronium bromide. 1. The effects of glycopyrrolate and pyridostigmine. *Curr Ther Res* 18:377-386, 1975
2. Ravin MB: Pyridostigmine as an antagonist of d-tubocuranrine-induced and pancuronium-induced neuromuscular blockade. *Anesth Analg—Curr Res* 54:317-321, 1975.

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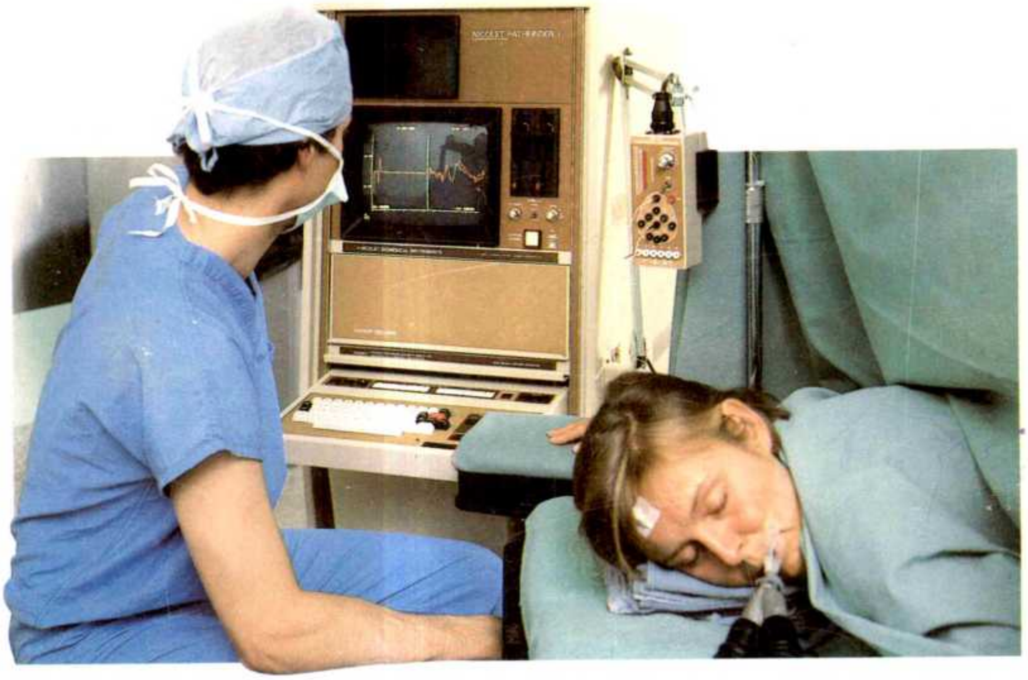

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WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

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PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous

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doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were: *Cardiovascular:* tachycardia, arrhythmia; *Gastrointestinal:* nausea, vomiting; *Respiratory:* apnea, postoperative respiratory depression, bronchospasm; *Dermatological:* itching, erythema; *Central Nervous System:* chills; *Miscellaneous:* intraoperative muscle movement.

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

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Patients receiving INOCOR should be carefully monitored with the following laboratory studies: platelet counts, liver enzymes, fluid and electrolyte changes, and renal function. Hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

1. Benotti JR, Grossman W, Braunwald E, et al: Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive heart failure due to coronary artery disease. *Circulation* 1980;62:28-34.

Please see brief summary of product information on this page for contraindications, adverse reactions, patient selection, and precautionary recommendations.

Winthrop
PHARMACEUTICALS

Winthrop Pharmaceuticals, Division of Sterling Drug Inc., New York, NY 10016

61065

INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

INDICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-term management of congestive heart failure in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators.)

INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness.

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites.

PRECAUTIONS *General:* INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

LABORATORY TESTS *Fluid and electrolytes:* Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metoprolol, propranolol, hydralazine, prazosin, isosorbide dinitrate, nitroglycerine, chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, potassium supplements, insulin, diazepam.

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace* disopyramide should be undertaken with caution.

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for use in acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been established.

USE IN PREGNANCY *Pregnancy category C.* In New Zealand white rabbits, amrinone has been shown to produce fetal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm this finding.[1] No malformations were seen in rats receiving amrinone intravenously at the maximum dose used 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN NURSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

ADVERSE REACTIONS *Thrombocytopenia:* Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm^3 in 2.4% of patients.

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Cardiovascular effects: Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%).

Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and ascites (one case); myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (one case); and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged, so attribution to amrinone is not certain, but possible hypersensitivity reactions should be considered in any patient maintained for a prolonged period on amrinone.

General: Additional adverse reactions observed in intravenous amrinone clinical studie include fever (0.9%), chest pain (0.2%), and burning at the site of injection (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotensio because of its vasodilator effect. If this occurs, amrinone administration should b reduced or discontinued. No specific antidote is known, but general measures f circulatory support should be taken.

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductions:* Asympt matic platelet count reduction (to less than 150,000/mm^3) may be reversed within on week of a decrease in drug dosage. Further, with no change in drug dosage, the cour may stabilize at lower than predrug levels without any clinical sequelae. Predrug platel counts and frequent platelet counts during therapy are recommended to assist decisions regarding dosage modifications.

Should a platelet count less than 150,000/mm^3 occur, the following actions may b considered:

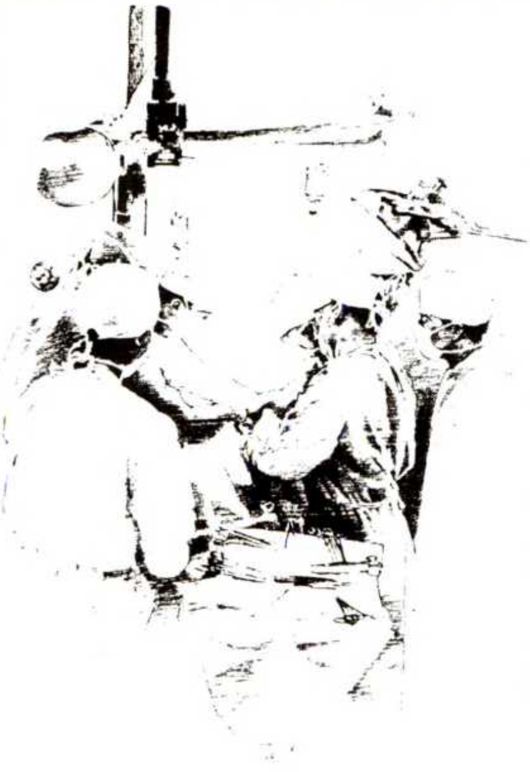
- Maintain total daily dose unchanged, since in some cases counts have eith stabilized or returned to pretreatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds th potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were seen infrequent with IV therapy, should severe or debilitating ones occur, the physician may wish reduce dosage or discontinue the drug based on the usual benefit-to-ris considerations.

Hepatic toxicity: In clinical experience to date with IV administration, hepatotoxicity h rarely been observed. If acute marked alterations in liver enzymes occur together w clinical symptoms, suggesting an idiosyncratic hypersensitivity reaction, amrino therapy should be promptly discontinued.

If less than marked enzyme alterations occur without clinical symptoms, the nonspecific changes should be evaluated on an individual basis. The clinician may w to continue amrinone and reduce the dosage or discontinue the drug based on the usu benefit-to-risk considerations.

HOW SUPPLIED Ampuls of 20 mL sterile, clear yellow solution containing INOC 5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOCOR lactate equ lent to 5-mg base and 0.25 mg sodium metabisulfite in water for injection.



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  "Edrophonium may in fact be the preferred reversal agent for routine use with [vecuronium], having the advantages that restoration of voluntary muscle function is very rapid, and that the relatively small dose of atropine required minimizes the unwanted side-effects of this drug."[4]

***Note:** When duration of action is adjusted for differences in onset of action, the relative durations are 65 minutes for edrophonium and 69 minutes for neostigmine.

1. Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. Anesthesiology 57:261-266, 1982. 2. Miller RD, et al: Comparative times to peak effect and duration of action of neostigmine and pyridostigmine. Anesthesiology 41:27-33, 1974. 3. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. Br J Anaesth 56:453-457, 1984. 4. Baird WLM, Bowman WC, Kerr WJ: Some actions of ORG NC45 and of edrophonium in the anaesthetized cat and in man. Br J Anaesth 54:375-385, 1982.

Please see use information on next page.

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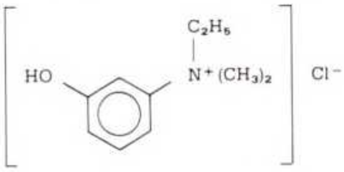
Enlon® (edrophonium chloride injection, USP)

DESCRIPTION

ENLON (edrophonium chloride injection, USP) is a rapid acting cholinergic (cholinesterase inhibitor). Chemically edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride and its structural formula is:



ENLON contains in each mL of sterile solution.

10 mg edrophonium chloride compounded with 0.45% phenol and 0.2% sodium sulfite as preservative, buffered with sodium citrate and citric acid. Its pH is adjusted to approximately 5.4.

CLINICAL PHARMACOLOGY

ENLON (edrophonium chloride injection, USP) activates neuromuscular transmission primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed by acetylcholinesterase and is thereby allowed to accumulate. The accumulation of acetylcholine at the sites of cholinergic transmission facilitates transmission of impulses across the myoneural junction.

INDICATIONS AND USAGE

ENLON (edrophonium chloride injection, USP) is recommended as a reversal agent or antagonist of nondepolarizing muscle relaxants such as tubocurarine, metocurine, atracurium, vecuronium, or pancuronium. It is not effective against depolarizing relaxants such as succinylcholine and decamethonium. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdosage.

ENLON is recommended for use in the differential diagnosis of myasthenia gravis. It may also be used as an adjunct to evaluate treatment requirements of the disease, and for evaluating emergency treatment in myasthenic crisis. It is not recommended for maintenance therapy in myasthenia gravis.

CONTRAINDICATIONS

ENLON (edrophonium chloride injection, USP) is not to be used in patients with known hypersensitivity to anticholinesterase agents, or in patients having urinary obstructions of mechanical type.

WARNINGS

It is recommended that 1 mg atropine sulfate should be made available for immediate use, to counteract any severe cholinergic reaction. ENLON (edrophonium chloride injection, USP) should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vagotonic effects.

PRECAUTIONS

General: As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance. Should a patient develop "anticholinesterase insensitivity" for brief or prolonged periods, the patient should be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them.

Drug Interactions: The drug should not be administered prior to the administration of any nondepolarizing muscle relaxants. The drug should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdosage (cholinergic crisis) symptoms may mimic underdosage (myasthenic weakness) so the use of this drug may worsen the condition of these patients (see OVERDOSAGE section for treatment).

Pregnancy Category C: It is not known whether ENLON (edrophonium chloride injection, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, since there have been no adequate and well controlled studies in humans.

Labor and Delivery: The effect of ENLON on the mother and fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary is not known. The effect of the drug on the later growth, development and functional maturation of the child is also unknown.

Nursing Mothers: The safety of ENLON during lactation in humans has not been established.

ADVERSE REACTIONS

A patient in myasthenic crisis, being treated with ENLON (edrophonium chloride injection, USP) should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdosage is given. Reactions common to anticholinesterase agents such as edrophonium chloride are:

Cardiovascular: arrhythmias (especially bradycardia), fall in output leading to hypotension;

Respiratory: increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

Neurologic: convulsions, dysarthria, dysphonia, and dysphagia;

Gastrointestinal: nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps;

Musculoskeletal: weakness and fasciculations;

Miscellaneous: increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia.

OVERDOSAGE

Muscarine-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) may appear with overdosage (cholinergic crisis) of ENLON (edrophonium chloride injection, USP) but may be managed by the use of atropine. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Signs of atropine overdosage such as dry mouth, flush and tachycardia should be avoided as tenacious secretions and bronchial plugs may form. Should edrophonium chloride overdosage occur:

1. Maintain respiratory exchange.
2. Monitor cardiac function.

Appropriate measures should be taken if convulsions or shock are present.

DOSAGE AND ADMINISTRATION

The recommended adult intravenous injection for antagonism of neuromuscular block:

Administer 1 mL (10 mg) slowly within a period of 30 to 45 seconds, the dosage may be repeated to a maximum total dose of 4 mL (40 mg). Its onset of action is manifest within 30 to 60 seconds after injection. Response should be monitored carefully and assisted ventilation should always be employed. When given to counteract muscle relaxant overdosage, the dose effect on respiration should be observed prior to repeat dosages and assisted ventilation should be employed.

ENLON (edrophonium chloride injection, USP) Test in Differential Diagnosis of Myasthenia Gravis:

Adults:

Intravenous Dosage: Prepare a tuberculin syringe with 1 mL (10 mg) of ENLON and an intravenous needle; intravenously inject 0.2 mL (2 mg) within 15 to 30 seconds. The needle should be left in situ. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs, discontinue test and intravenously administer 0.4 mg to 0.5 mg atropine sulfate. Inject the remaining 0.8 mL (8 mg) only if no reaction occurs after 45 seconds. The test may be repeated after one-half hour.

Intramuscular Dosage: Intramuscularly inject 1 mL (10 mg) of ENLON. If hyperreactivity (cholinergic reaction) is demonstrated, retest the patient after one-half hour with another intramuscular injection of 0.2 mL (2 mg) ENLON. This will eliminate the possibility of false-negative reactions.

Children:

Intravenous dose in children weighing up to 75 pounds:

Intravenously inject 0.1 mL (1 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 0.5 mL (5 mg). The recommended dose in infants is 0.05 mL (0.5 mg).

Intravenous dose in children weighing above 75 pounds:

Intravenously inject 0.2 mL (2 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 1 mL (10 mg).

Intramuscular Dose: Intramuscularly inject 0.2 mL (2 mg) ENLON in children weighing up to 75 pounds; above this weight, the dose is 0.5 mL (5 mg). All signs of hyperreactivity (cholinergic reaction) noted in the intravenous test will be demonstrated in the intramuscular test; however, there is a two to ten minute delay before reaction.

ENLON (edrophonium chloride injection, USP) Test to Evaluate Treatment Requirements in Myasthenia Gravis:

The test dose of ENLON should follow one hour after oral intake of the drug being used to treat the disease. The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) administered intravenously. Response to ENLON test dose in treated myasthenic patients is summarized as follows:

Undertreated patient: Myasthenic response; characterized by increased muscle strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength). This indicates inadequate treatment of the myasthenic condition.

Controlled patient: Adequate response; characterized by no change in muscle strength with minimal side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea). Fasciculations (orbicularis oculi, facial muscles, limb muscles) may or may not occur. The response indicates that therapy is stabilized.

Overtreated patient: Cholinergic response; characterized by decreased muscle strength and severe side reactions. Fasciculations may be observed. This response occurs in myasthenics who have been overtreated with anticholinesterase drugs.

ENLON (edrophonium chloride injection, USP) Test in Crisis:

Crisis in the myasthenic patient is characterized as a state of severe respiratory distress with inadequate ventilatory exchange, and unpredictable response to medication. If the patient is apneic, achieve ventilatory exchange immediately to avoid cardiac arrest and irreversible central nervous system damage.

The ENLON Test should not be conducted until respiratory exchange is maintained. The cholinergic patient will exhibit further weakness in the muscles of respiration and will have increased oropharyngeal secretions if ENLON is administered. Whereas, upon administration of ENLON the myasthenic patient will demonstrate improved respiration and can be given additional medication. To perform the test prepare a syringe with 0.2 mL (2 mg) ENLON and intravenously inject 0.1 mL (1 mg). The patient's cardiac and respiratory actions should be observed for change. The remaining 0.1 mL (1 mg) may be injected after one minute if no response is noted. If, after the entire 0.2 mL (2 mg) dose has been injected, no improvement in respiration occurs, discontinue all anticholinesterase drugs. Controlled ventilation can be achieved by tracheostomy with assisted respiration.

HOW SUPPLIED

ENLON (edrophonium chloride injection, USP):

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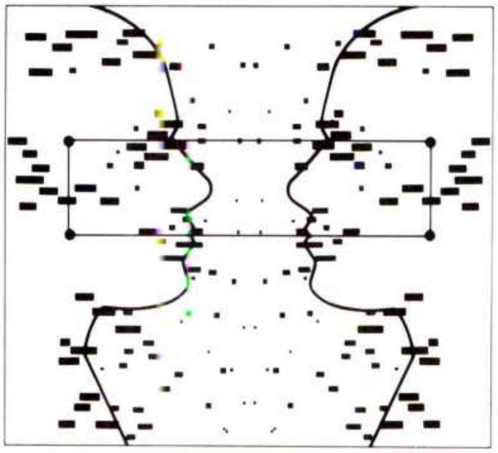

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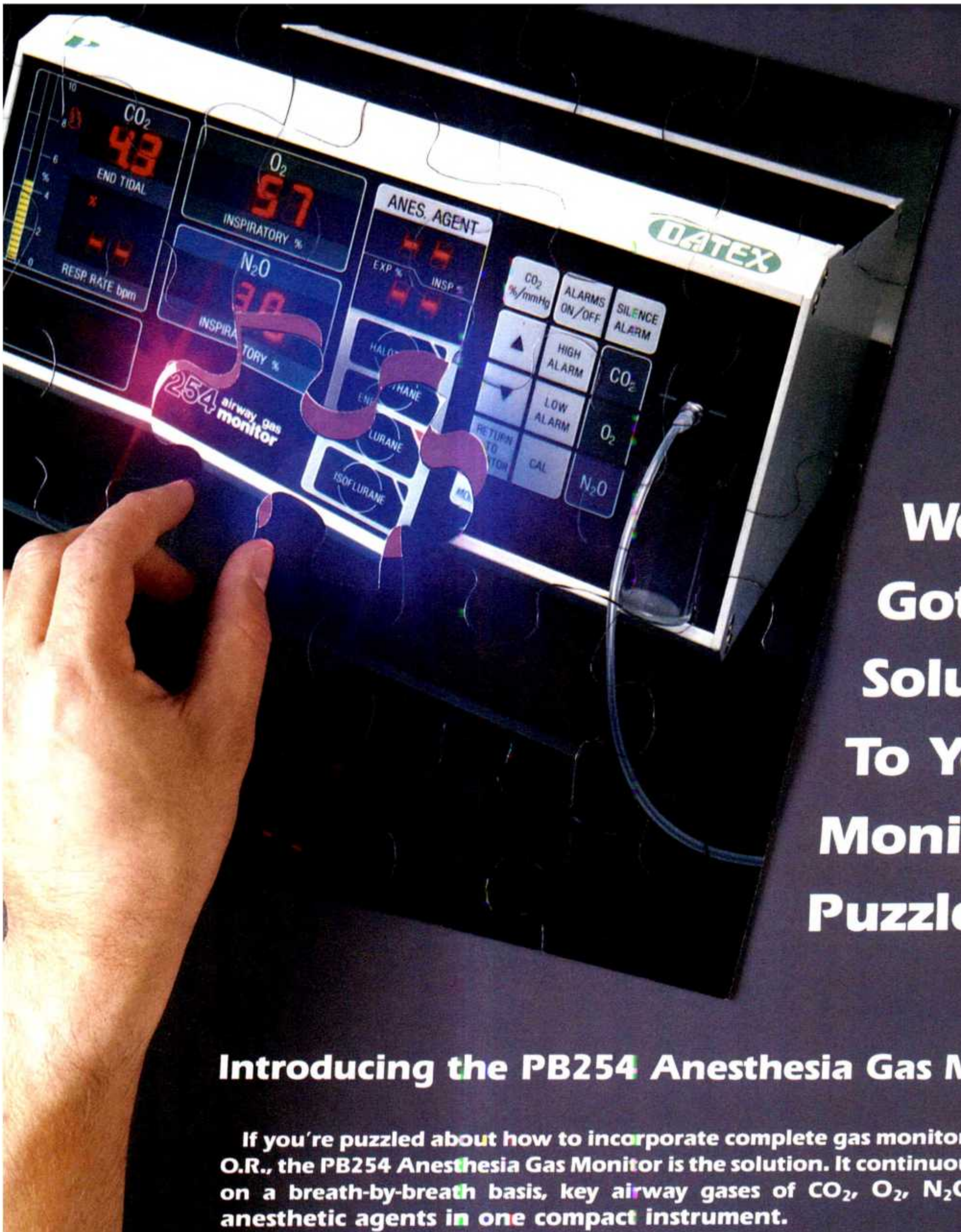

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ANESTH ANALG
1987;66:103–10

Cardiovascular Function during Controlled Hypotension Induced by Adenosine Triphosphate or Sodium Nitroprusside in the Anesthetized Dog

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KIEN ND, WHITE DA, REITAN JA, EISELE JH Jr. Cardiovascular function during controlled hypotension induced by adenosine triphosphate or sodium nitroprusside in the anesthetized dog. Anesth Analg 1987;66:103–10.

The present study was undertaken to compare the hemodynamic effects of adenosine triphosphate (ATP) and sodium nitroprusside (NP) given in equieffective doses to induce hypotension during halothane anesthesia. Eight dogs, instrumented with pressure and ultrasonic dimension transducers for assessment of left ventricular (LV) performance, were given both NP and ATP. Regional blood flow was measured by radioactive microspheres. After 20 min of infusion, both drugs decreased systemic arterial pressure by 36% with minimal changes in cardiac index (CI), LV end-diastolic pressure, or heart rate. However, hypotension produced by ATP was associated with a greater CI (3.84 ± 0.32 vs 2.97 ± 0.35 L·min^{-1}·m^{-2}) than was NP and also associated with a further decrease in systemic vascular resistance (14.4 ± 1.4 vs 17.7 ± 2.2 mm Hg·L^{-1}·min·m^{2}). Left ventricular global function, measured by the slope of the linear regression line of the LV end-systolic pressure-diameter relation (Ees), did not change significantly after either drug. Blood flow to the coronary bed was significantly greater with ATP than with NP (231.6 ± 30.6 vs 81.7 ± 6.1 ml·min^{-1}·100 g^{-1}). Except for an increase in hepatic arterial blood flow with NP, neither ATP nor NP significantly altered blood flow to the brain, spinal cord, spleen, kidney, jejunum, muscle, and skin. Controlled hypotension by ATP was stable and rapidly reversible without rebound hypertension. The results of this study indicate that ATP is a rapidly acting, effective hypotensive agent that compares favorably with NP.

Key Words: ANESTHETIC TECHNIQUES—hypotensive.

Vasodilators have been used to induce hypotension during anesthesia for reduction of intraoperative blood loss and improvement of the surgical field. Among the drugs used to induce hypotension, sodium nitroprusside (NP) has been most popular because of its potency and relatively short half-life. However, NP may be associated with cyanide toxicity, rebound hypertension, and tachyphylaxis (1–3). Recently, adenosine triphosphate (ATP) has been advocated as a hypotensive agent because of its potent vasodilatory effect in most vascular beds (4,5). Because the safety of clinical hypotension depends on myocardial performance and the adequacy of blood supply to various organs, this study was designed to compare the effects of equihypotensive doses of ATP and NP on left ventricular function and peripheral blood flow in dogs during halothane anesthesia.

Methods

Surgical Preparation

Eight mongrel dogs (either sex) (20–27 kg) were anesthetized with thiamylal, 15 mg/kg IV, intubated, and ventilated using a positive-pressure Harvard respirator. Anesthesia was maintained with 1.5% halothane in oxygen. A semirigid catheter was inserted into the thoracic aorta via the femoral artery. Cardiac output was measured by thermodilution using a pulmonary artery catheter and an Edward's computer (Model 9520 A), with iced saline as the indicator. Through a left thoracotomy at the fifth intercostal space, the pericardium was opened and a flexible polyethylene catheter inserted into the left atrium via the appendage for pressure measurements and injection of radioactive microspheres. Left ventricular (LV) pressure was measured with a Königsberg miniature

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Presented in part at the 69th Annual Meeting of the Federation of American Societies for Experimental Biology Anaheim, California, April 21–26, 1985.

Received from the Department of Anesthesiology, University of California, School of Medicine, Davis, California. Accepted for publication August 25, 1986.

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transducer secured in the left ventricle via a stab wound in the apex. Left ventricular end-diastolic pressure and dP/dt were derived from the LV pressure tracing. The Königsberg transducer was calibrated in vitro against a mercury manometer and in vivo against aortic systolic pressure and left atrial pressures. Frequent calibration was made to eliminate the electrical drift of this transducer. Blood pressure was measured with a Statham P-23 Db strain gauge. Pulse-transit ultrasonic dimension transducers were implanted in pairs 1) on the epicardium across the anterior–posterior minor axis to measure the transverse external diameter, 2) into the anterior lateral free wall to measure the segmental length in the plane of the minor axis, and 3) on the epicardium and opposite endocardium of the lateral free wall to measure wall thickness. Proper alignment of these transducers was confirmed with a high-frequency oscilloscope (Textronix, RM 647). Myocardial motions were monitored with a multichannel sonomicrometer (Triton Technology, 120). Inflatable balloon occluders were placed around both vena cavae to vary preload during assessment of LV contractility. Blood temperature was measured continuously and maintained at 37°C with heating pads. Hemodynamic data and ventricular dimensions were recorded on a direct-writing recorder (Gould, 2800 S) and on F-M magnetic tape (Ampex, SP-300) for subsequent analysis.

Measurement of Distribution of Peripheral Blood Flow

Regional blood flow was measured with radioactive microspheres. The microspheres (15 μm) labeled with ^{51}Cr, ^{141}Ce, or ^{85}Sr (3M Co.) were suspended in 10% dextran and 0.01% Tween-80. Prior to the injection, the microspheres were placed into an ultrasonic bath for 15 min and vigorously agitated using a mechanical mixer to ensure dispersion. Microscopic examination was used to confirm the absence of microsphere aggregation. For each new batch of microspheres, the supernatant solution was injected to assure that no adverse effect on physiologic measurements was caused (6,7). Approximately 2–3 × 10^6 microspheres in 0.5-ml aliquots were injected over a 20-sec period and flushed in 4 ml of 37°C saline. Reference blood flow samples were withdrawn from a femoral catheter starting 15 sec before the microsphere injection and continuing for 2 min at a constant rate of 7.75 ml/min.

At the end of the experiment, the dogs were killed with a halothane overdose and intravenous injection of saturated KCl. The sampled organs were then removed, cleaned of fat and attached vessels, sectioned, weighed, and counted for radioactivity at appropriate energy windows by means of a multichannel pulse-height analyzer. In the heart, a one-half inch thick cross section of the left ventricle at the middle distance from the base to the apex was sampled. The free wall was divided into three different layers of equal thicknesses: epicardium, midwall, and endocardium. Cortical samples were taken for measurements of blood flow to the brain and kidney; the muscle sample was collected from the biceps femoris. The spinal cord was sampled in a two-inch segment at the thoracic region. Samples were also taken from the spleen, liver, jejunum and skin.

Experimental Protocols

After completion of instrumentation, the end-tidal halothane concentration was reduced to 0.75% (1 MAC) measured by a calibrated monitor. Experiments were conducted 15 min after instrumentation when cardiovascular stability was present and arterial blood gas tensions were normal. Whereas all pressures and LV dimensions were monitored continuously, cardiac output was averaged from intermittent triplicate measurements. Cardiac contractility was assessed during vena caval occlusion using the slope of the linear regression of the LV end-systolic pressure–diameter relation. To eliminate any respiratory influence on hemodynamic measurements, cardiac contractility was assessed while the respirator was turned off momentarily. Autonomic sympathetic reflex caused by vena caval occlusion was minimized by eliminating heart beats with R-R intervals varying more than 10% from the preocclusion interval.

After the first baseline recordings, NP was infused at 5 μg·kg^{-1}·min^{-1} by means of a variable speed Harvard infusion pump and recordings were made after 20 min of infusion. A 60 min rest period was then allowed for recovery.

After a second baseline recording, ATP was infused at 1 mg·kg^{-1}·min^{-1} and recordings were repeated as above. Microspheres were injected during the initial baseline and at 20 min of the NP and ATP infusions. The sequence of microspheres and the order of NP and ATP were alternated randomly so that each dog served as its own control. If the difference between the two baselines was larger than 5%, the experiment was invalidated and its data discarded.

Calculations

Regional blood flow (RBF) was calculated in ml·min^{-1}·100 g^{-1} using the following formula: RBF = 100 × Ct × Qr/Cr × Wt, where Ct and Cr are radioactive counts of tissue sample and reference blood

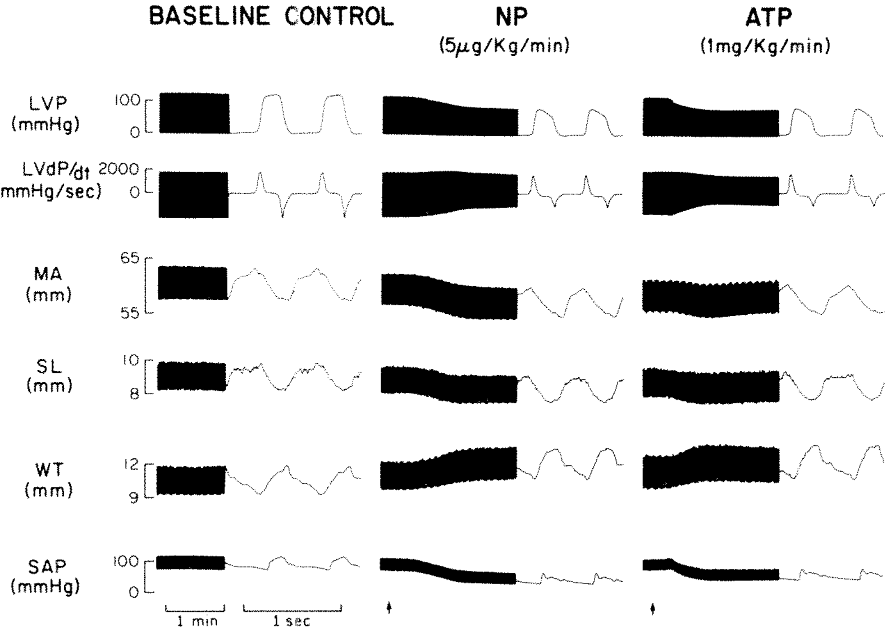

Figure 1. Representative recordings in one dog illustrate the immediate effects of NP and ATP. Arrows indicate onset of infusions with time scales at the bottom. At equal hypotensive levels, similar responses are observed except for a more rapid onset of action and a greater systolic change in wall thickness with ATP. Abbreviations: LVP, left ventricular pressure; LVdp/dt, first derivative of left ventricular pressure tracing; MA, minor axis; SL, segmental length; WT, wall thickness; SAP, systemic arterial pressure.

respectively; $\dot{Q}r$ and Wt are reference flow rate and tissue sample weight. Radioactive counts of tissue samples in counts per minute were computer corrected for background and crossover energy between the isotopes by means of standard stripping formulas. From the measurements of myocardial perfusion, we calculated the transmural distribution of blood flow (endocardial/epicardial flow ratio) and endocardial flow/wall stress ratio.

Hemodynamic values were averaged from data obtained during the steady state recording periods. Fifteen consecutive heart beats with no apparent arrhythmia were analyzed at end-systole. For each heart beat, end-systole was defined as 20 msec before the peak negative LVdP/dt and end-diastole was assumed at the beginning of the rapid rise in LVP after atrial systole. The LV end-systolic pressure–diameter relation was evaluated using the equation: $P = Ees\ (D - D_d)$, where P and D are LV end-systolic pressure and diameter respectively, D_d is the intercept of the diameter axis, and Ees is the slope of the linear regression line connecting the end-systolic points of the pressure–diameter relations at various ventricular loading levels. Percent systolic shortening was calculated as the percent of systolic dimension change divided by the end-diastolic dimension.

The LV end-systolic meridional wall stress was calculated as described by Colan et al. (8):

$$\sigma\ es = \frac{1.35\ P{\cdot}Di}{4(h)\ (1 + h/D)}$$

where σ es is LV end-systolic meridional wall stress in g/cm^2, and P, Di, and h are pressure, internal diameter, and wall thickness of the left ventricle at end-systole, respectively.

Data from eight dogs were summarized as mean ± SEM. Hemodynamic changes during NP and ATP infusion were expressed as percent change from control. Statistical analysis of data included analysis of variance and Student's *t*-tests for paired data. Probability values less than 0.05 were considered statistically significant.

The use of the animals was approved by the University's animal care committee. All animals received care in compliance with the "Principles of Laboratory Animal Care," formulated by the National Society for Medical Research, and the "Guide for the Care and Use of Animals," prepared by the National Academy of Sciences, and published by the National Institutes of Health (NIH Publication No. 80-23, revised 1978).

Results

Hypotension induced with ATP was rapid in onset, stable, and easily reversible. A steady state blood pressure was obtained 3.1 ± 0.2 min after onset of the ATP infusion compared to 6.3 ± 0.5 min with NP ($P < 0.01$). Upon termination of infusion, return of blood pressure to control was significantly more rapid with ATP than NP (4.1 ± 0.3 vs 15.9 ± 2.4 min with NP). Blood gas tensions in two dogs showed no evidence of metabolic acidosis at any time during the hypotensive period. Analog recordings obtained during baseline and hypotensive periods in one dog are

Table 1. Effects of Sodium Nitroprusside and Adenosine Triphosphate on Baseline Hemodynamics

	Baseline	Sodium Nitroprusside	Baseline	Adenosine Triphosphate
HR (beats/min)	102 ± 5	110 ± 5	103 ± 6	102 ± 4
SAP (mm Hg)	91 ± 4	58 ± 4[a]	88 ± 7	59 ± 4[a]
LVP (mm Hg)	104 ± 6	77 ± 5[a]	103 ± 4	82 ± 4[a]
LVdP/dt (mm Hg/sec)	1794 ± 39	1417 ± 78[a]	1729 ± 156	1872 ± 91[b]
CI ($L \cdot min^{-1} \cdot m^{-2}$)	3.28 ± .35	2.97 ± .35	3.37 ± .21	3.84 ± .32[b]
SVI ($ml \cdot beat^{-1} \cdot m^{-2}$)	29.0 ± 3.0	25.5 ± 2.7	29.4 ± 2.1	33.1 ± 2.7[b]
SVRI ($mm\ Hg \cdot L^{-1} \cdot min \cdot m^2$)	28.6 ± 3.4	17.7 ± 2.2[a]	25.8 ± 2.7	14.4 ± 1.4[a,b]
PAP (mm Hg)	15.6 ± .8	14.0 ± 1.0	15.1 ± 1.1	13.9 ± 1.2
LVEDP (mm Hg)	8.1 ± .7	7.1 ± .3	7.8 ± .4	8.0 ± .4
WS (g/cm^2)	46.6 ± 6.7	24.2 ± 3.7[a]	46.8 ± 6.1	23.9 ± 3.7[a]
Ees (mm Hg/mm)	12.2 ± .8	11.2 ± 1.5	12.0 ± 2.3	13.9 ± 2.1
MA (%SS)	7.0 ± .6	7.8 ± .5	7.3 ± .5	8.2 ± .5
SL (%SS)	14.0 ± 2.2	14.4 ± 2.0	13.9 ± 2.7	17.0 ± 7.8
WT (%ST)	14.1 ± 2.6	12.5 ± 1.6	13.9 ± 1.1	15.6 ± 1.7[b]

Values represent the mean ± SEM of eight dogs.

Abbreviations: HR, heart rate; SAP, systemic arterial pressure; LVP, left ventricular pressure; LVdp/dt, first derivative of left ventricular pressure tracing; CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistance index; PAP, pulmonary artery pressure; LVEDP, left ventricular end-diastolic pressure; WS, left ventricular end-systolic meridional wall stress; Ees, slope of the left ventricular end-systolic pressure–diameter relation; MA, minor axis; %SS, percent of systolic shortening; SL, segmental length; WT, wall thickness; %ST, percent of systolic thickening.

[a] $P < 0.05$ compared to control.

[b] $P < 0.05$ compared to sodium nitroprusside.

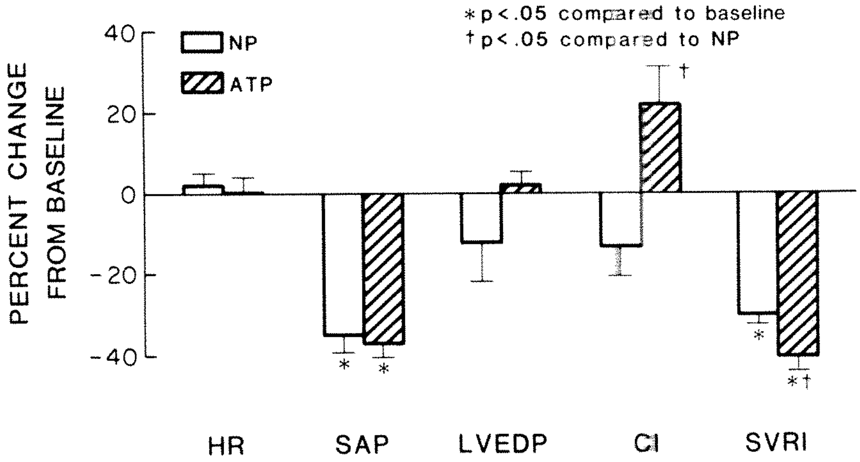

Figure 2. Comparison of the hemodynamic responses to NP and ATP. Changes are expressed in percent from control. Note significant differences in CI and SVRI. Bars represent mean ± SEM. Abbreviations: HR, heart rate; SAP, systemic arterial pressure; LVEDP, left ventricular end-diastolic pressure; CI, cardiac index; SVRI, systemic vascular resistance index.

shown in Figure 1. Systemic arterial and LV pressures are displayed along with the minor axis diameter, segmental length, and wall thickness dimensions. Similar responses were observed after infusion of either ATP or NP. Table 1 summarizes the hemodynamic data obtained as baseline measurements and during hypotension. There was no significant difference between the baseline values before administration of the two drugs.

After 20 min of infusion with either ATP or NP, systemic arterial pressure decreased an average of 36.4% below baseline levels without significant changes in heart rate or LV end-systolic pressure (Fig. 2). During ATP infusion, the stroke volume index was 30% greater than that during NP. Because there was no change in heart rate, the increase in stroke volume index paralleled the increase in cardiac index observed with ATP. Calculated systemic vascular resistance was significantly lower with ATP than with NP (14.4 ± 1.4 vs 17.7 ± 2.2 mm $Hg \cdot L^{-1} \cdot min \cdot m^2$).

The effects of ATP and NP on myocardial performance are shown in Figure 3. Percent fiber shortening of the minor axis, segmental length, and wall thickness and the global performance of the left ventricle measured by Ees during induced hypotension were not significantly different from baseline values. However, percent systolic thickening of the LV free wall increased significantly with ATP compared to NP (15.6

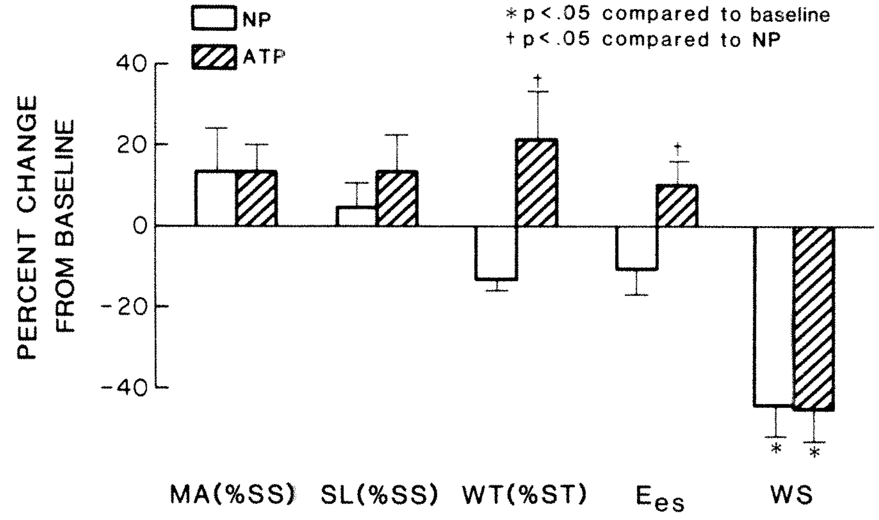

Figure 3. Comparison of the hypotensive effects induced by NP and ATP on myocardial performance. Changes are expressed in percent from control. Percent of systolic thickening is significantly greater after ATP as compared to NP. Bars represent mean ± SEM. Abbreviations: MA, minor axis; SL, segmental length; WT, wall thickness; Ees, slope of the left ventricular end-systolic pressure–diameter relation; WS, left ventricular end-systolic meridional wall stress.

Table 2. Myocardial Blood Flow during Hypotension Induced by Sodium Nitroprusside and Adenosine Triphosphate

	Baseline	Sodium nitroprusside	Adenosine triphosphate
Heart (average)	72.8 ± 7.6	81.7 ± 6.1	231.6 ± 30.6^{a,b}
LV endocardium	86.3 ± 7.7	95.0 ± 5.6	282.6 ± 30.9^{a,b}
LV epicardium	79.5 ± 10.6	81.5 ± 9.1	210.7 ± 17.6^{a,b}
Endocardium/Epicardium	1.08 ± 0.13	1.17 ± 0.10	1.62 ± 0.22^{a,b}
Endocardium/WS	1.75 ± 0.21	3.82 ± 0.88^{a}	11.21 ± 1.92^{a,b}

Values represent the mean ± SEM of eight dogs and are expressed in ml·min^{-1}·100gr^{-1}.
Abbreviations: LV, left ventricular; WS, left ventricular end-systolic meridional wall stress.
[a] $P < 0.05$ compared to control.
[b] $P < 0.05$ compared to sodium nitroprusside.

± 1.7 vs 12.5 ± 1.6%, respectively). Left ventricular end-systolic meridional wall stress decreased an average of 45%, indicating similar reductions in myocardial oxygen consumption during ATP or NP infusion.

Myocardial blood flows measured before and during hypotension are shown in Table 2. During NP infusion, myocardial blood flow and the endocardial/epicardial flow ratio were not significantly different from baseline levels. In contrast, during ATP infusion, myocardial blood flow increased threefold and the endocardial/epicardial flow ratio increased 40%. The balance between myocardial oxygen supply and demand was examined by the ratio of endocardial flow to wall stress. This ratio doubled from control with NP but increased six times with ATP.

Table 3 shows the effects of NP and ATP on organ blood flow. During infusion of NP, hepatic arterial flow increased from 16.0 ± 4.7 to 33.7 ± 6.8 ml·min^{-1}·100 g^{-1}. Such an increase in hepatic arterial flow was not observed during infusion of ATP. Blood flow to the cerebral cortex, spinal cord, spleen, renal cortex, jejunum, muscle, and skin was unchanged during hypotension produced by either agent.

Discussion

Various techniques have been employed to reduce arterial pressure when excessive intraoperative hemorrhage occurs (9). Although many organs have vascular autoregulatory mechanisms, the maintenance of normal perfusion may be altered under anesthesia or when arterial pressure decreases below a critical level. Because this critical level varies among organs and may be different among individuals, it is difficult to define a safe lower limit for blood pressure during induced hypotension. Nevertheless, clinically, induced hypotension is maintained most often at a mean arterial pressure of 60 mm Hg to avoid the pressure dependency of some organ blood flows when arterial pressure decreases below this level.

In this study, our purpose was to compare the hemodynamic effects of ATP and NP at doses sufficient to reduce mean arterial pressure to 60 mm Hg. Previous investigations of ATP and NP have concentrated primarily on systemic effects; the specific effects of these vasodilators on myocardial performance have not been thoroughly examined. Using sonomicrometry, dimensions of the left ventricle were mon-

Table 3. Organ Blood Flows during Hypotension Induced by Sodium Nitroprusside and Adenosine Triphosphate

	Baseline	Sodium nitroprusside	Adenosine triphosphate
Cerebral cortex	53.1 ± 5.6	56.9 ± 5.2	51.4 ± 7.4
Spinal cord	15.7 ± 3.7	15.6 ± 5.2	18.5 ± 2.8
Spleen	123.8 ± 21.6	126.6 ± 25.5	138.9 ± 20.3
Hepatic arterial flow	16.0 ± 4.7	33.7 ± 6.8^a	18.9 ± 5.3^b
Renal cortex	501.3 ± 33.1	533.0 ± 54.3	454.5 ± 14.5
Jejunum	102.9 ± 11.4	104.7 ± 10.6	94.5 ± 15.7
Muscle	4.0 ± 0.6	4.4 ± 0.6	4.2 ± 0.8
Skin	1.9 ± 0.3	1.7 ± 0.2	1.4 ± 0.2

Values represent the mean ± SEM of eight dogs and are expressed in $ml \cdot min^{-1} 100g^{-1}$.
$^a P < 0.05$ compared to control.
$^b P < 0.05$ compared to sodium nitroprusside.

itored in the present study simultaneously with the measurement of the left ventricular pressure (LVP) for the assessment of myocardial performance. Whereas the change in regional performance was evaluated from the percent of systolic shortening, the slope of the LV end-systolic pressure–diameter relations generated during vena caval occlusion was used as an index of global change in contractility. This slope is independent of loading conditions and closely related to the inotropic state of the heart (10–13). The results indicate that myocardial performance was not altered significantly by either ATP or NP at the hypotensive level employed in this study. In fact, as compared to NP, cardiac contractility was greater with ATP. This is in contrast to the negative inotropic effects reported when adenine compounds were administered to isolated mammalian hearts (14–16).

Both ATP and NP caused rapid reduction in arterial pressure. This reduction was attributed mainly to a decrease in peripheral resistance secondary to arterial vasodilation. Systemic vascular resistance was significantly lower with ATP than with NP, indicating that ATP exerted a more profound vasodilator effect on the peripheral vasculature. In parallel to the afterload reduction, stroke volume increased markedly during ATP infusion, which resulted in a higher cardiac output than that seen with NP. The difference in cardiac output between ATP and NP may be a result of the greater decrease in peripheral resistance caused by ATP or because of venodilation with a decrease in venous return produced by NP (17).

Although NP did not have a significant influence on coronary blood flow, ATP increased coronary flow by threefold and altered the endocardial/epicardial flow ratio in favor of the endocardial layer, indicating the potency of the vasodilator effect of ATP in the coronary bed. In fact, the ratio of endocardial blood flow to wall stress, which reflects endocardial oxygen supply/demand ratio, increased sixfold with ATP infusion. Apparently ATP provides luxury perfusion in the endocardial layer.

Our findings show that hypotension induced by either ATP or NP was not associated with a change in heart rate. In conscious dogs with intact baroreflex mechanisms, infusion of NP caused an immediate increase in heart rate with a corresponding decrease in arterial pressure (18). However, in anesthetized animals, no change in heart rate was observed at a dose of NP similar to that used in this study (19–21). In other investigations, increases in HR and plasma catecholamines levels were reported at high cumulative doses of NP, which suggested that enhanced sympathetic activity was responsible for the tachycardia observed when NP was infused for a longer period (22) or at a larger dose (23). Reports on the chronotropic responses to ATP, on the other hand, have not been consistent. Adenine compounds were found to inhibit norepinephrine release from sympathetic nerve endings (24), reduced atrioventricular node conduction velocity and elicited a negative chronotropic effect (25). In an isolated atrium preparation, Chiba et al. demonstrated that the chronotropic effect of ATP switched from negative to positive as the dose of ATP increased (26). Under halothane anesthesia, heart rate either decreased (4,5) or was maintained at baseline, as observed in this study, during ATP infusion; whereas tachycardia after ATP was reported with morphine and piritramide anesthesia (27,28). What exact influence anesthesia and dosage may have on the chronotropic effect of ATP in the intact animal is not clear.

Blood flow to the cerebral cortex did not change after administration of either ATP or NP, indicating that the cerebrovascular autoregulatory mechanisms remained intact at the level of hypotension studied. At a greater reduction of arterial pressure, ATP was reported to decrease cerebral blood flow in a dose-dependent fashion in baboons (29) and dogs (21,30).

Similar to the cerebral circulation, blood flow to the spinal cord, spleen, kidney, jejunum, muscle, and skin was well maintained during infusion of ATP and NP. This constancy of flow indicated that perfusion of these tissues was not pressure-dependent at an arterial pressure of 60 mm Hg. Apparently at this level of hypotension autoregulatory limits were not exceeded.

In this study, the hepatic arterial blood flow was unaltered by ATP, whereas it increased twofold during NP infusion. Because the radioactive microsphere technique measures the arterial perfusion of an organ, blood flow to the liver in our study only accounts for the hepatic arterial flow and does not include the portal venous inflow (31). The splanchnic circulation, which drains into the portal vein, is sympathetically innervated. Increases in plasma renin activity and circulating catecholamine levels associated with NP (22,32) may induce vasoconstriction in the splanchnic bed that, in turn, decreases portal venous inflow. Therefore, the increased flow to the liver observed during NP infusion is likely to be a result of the reciprocal mechanism of the hepatic vasculature, which dilates the hepatic artery in response to the portal vein restriction.

In summary, ATP and NP reduced arterial pressure by decreasing systemic vascular resistance. Cardiac output was greater with ATP than with NP because of an increase in stroke volume while heart rate did not change. Adenosine triphosphate produced a specific vasodilator effect on the coronary bed that was much more potent than that of NP. Except for an increase in hepatic arterial blood flow with NP, organ perfusion was not altered significantly when either ATP or NP was infused to reduce arterial pressure to 60 mm Hg. The results of this study indicate that ATP compares favorably with NP and may be an attractive agent for inducing clinical hypotension.

The authors thank Richard Martucci and Darcy Quam for their technical support, and Kathi Meuer for her secretarial assistance.

References

1. Cottrell JE, Patel K, Casthely P, Klein A, Turndorf H. Nitroprusside tachyphylaxis without acidosis. Anesthesiology 1978;49:141–2.
2. Michenfelder JD. Cyanide release from sodium nitroprusside in the dog. Anesthesiology 1977;46:196–201.
3. Khambatta HJ, Stone JG, Khan EM. Hypertension during anesthesia on discontinuation of sodium nitroprusside-induced hypotension. Anesthesiology 1979;51:127–30.
4. Fukunaga AF, Flacke WE, Bloor BC. Hypotensive effects of adenosine and adenosine triphosphate compared with sodium nitroprusside. Anesth Analg 1982;61:273–8.
5. Hoffman WE, Satinover I, Miletich DJ, Albrecht RF, Gans BJ. Cardiovascular changes during sodium nitroprusside or adenosine triphosphate infusion in the rat. Anesth Analg 1982;61:99–103.
6. Millard RW, Baig H, Vatner SF. Cardiovascular effects of radioactive microsphere suspensions and tween-80 solutions. Am J Physiol 1977;232:H331–4.
7. Baer RW, Payne BD, Verrier ED, Vlahakes GJ, Molodowitch D, Uhlig PN, Hoffman JIE. Increased number of myocardial blood flow measurements with radionuclide-labeled microspheres. Am J Physiol 1984;246:H418–34.
8. Colan SD, Borow KM, Newmann A. Left ventricular end-systolic wall stress-velocity of fiber shortening relation: A load-independent index of myocardial contractility. J Am Coll Cardiol 1984;4:715–24.
9. Adams AP. Techniques of vascular control for deliberate hypotension during anaesthesia. Br J Anaesth 1971;47:777–92.
10. Little WC, Freeman GL, O'Rourke RA. Simultaneous determination of left ventricular end-systolic pressure–volume and pressure–dimension relationships in closed-chest dogs. Circulation 1985;71:1301–8.
11. Mahler F, Covell JW, Ross J, Jr. Systolic power–diameter relations in normal conscious dog. Cardiovasc Res 1979;9:447–55.
12. Sagawa K, Suga H, Shoukas AA, Bakalar KM. End-systolic pressure–volume ratio: a new index of contractility. Am J Cardiol 1977;40:748–53.
13. Van Trigt P, Christian CC, Fagraeus L, et al. Myocardial depression by anesthetic agents (halothane, enflurane and nitrous oxide): quantitation based on end-systolic pressure–dimension relations. Am J Cardiol 1984;53:243–247.
14. Chiba S. Differences in chronotropic and inotropic responses of canine atrial muscle and SA node pacemaker activity to adenosine and ACh. Jap Heart J 1976;17:73–9.
15. De Gubareff T, Sleator W, Jr. Effects of caffeine on mammalian atrial muscle, and its interaction with adenosine and calcium. J Pharmacol Exp Ther 1965;148:202–14.
16. Buckley NM, Tsuboi KK, Zeig NJ. Inotropic effects of purines and pyrimidines on the isolated heart. Circ Res 1961;9:242–9.
17. Fouleur H, Covell JW, Ross J. Effects of nitroprusside on venous return and central blood volume in the absence and presence of heart failure. Circulation 1980;61:328–37.
18. Pagani M, Vatner SF, Braunwald E. Hemodynamic effects of intravenous sodium nitroprusside in the conscious dog. Circulation 1978;57:144–51.
19. Colley PS, Sivarajan. Regional blood flow in dogs during halothane anesthesia and controlled hypotension produced by nitroprusside or nitroglycerin. Anesth Analg 1984;63:503–10.
20. Wang HH, Liu LMP, Katz RL. A comparison of the cardiovascular effects of sodium nitroprusside and trimethaphan. Anesthesiology 1977;46:40–8.
21. Fan FC, Kim S, Simchon S, Chen RYZ, Schuessler GB, Chien S. Effects of sodium nitroprusside on systemic and regional hemodynamics and oxygen utilization in the dog. Anesthesiology 1980;53:113–20.
22. Bloor BC, Fukunaga AF, Ma C, Flacke WE, Ritter J, Etten AV, Olewine S. Myocardial hemodynamics during induced hypotension: a comparision between sodium nitroprusside and adenosine triphosphate. Anesthesiology 1985;63:517–25.
23. Sivarajan M, Amory DW, McKenzie SM. Regional blood flows during induced hypotension by nitroprusside or trimethaphan in the rhesus monkey. Anesth Analg 1985;64:759–66.
24. Verhaeghe RH, Vanhoutte PM. Inhibition of sympathetic neurotransmission in canine blood vessels by adenosine and adenine nucleotides. Circ Res 1977;40:208–15.
25. Belardinelli L, West A, Crampton R, Berne RM. Chronotropic

and dromotropic effects of adenosine. In: Berne RM, Rall TW, Rubio R, eds. Regulatory function of adenosine. Boston: Martinus/Nijoff, 1983:377–96.

26. Chiba S, Kobayashi M, Shimotori M. Chronotropic responses to large doses of adenosine and ATP in dog isolated atria. Japan J Pharmacol 1983;33:495–7.
27. Van Aken H, Puchstein CH, Anger C, Heinecke A, Lawin P. Changes in intracranial pressure and compliance during adenosine triphosphate-induced hypotension in dogs. Anesth Analg 1984;63:381–5.
28. Boarini DJ, Kassell NF, Sprowell JA, Olin JJ, Coester HC. Adenosine triphosphate-induced arterial hypotension in the dogs. Neurosurgery 1984;15:325–31.
29. Van Aken H, Puchstein C, Fitch W, Graham DI. Haemodynamic and cerebral effects of ATP-induced hypotension. Br J Anaesth 1984;56:1409–16.
30. Kassell NF, Boarini DJ, Olin JJ, Sprowell JA. Cerebral and systemic circulatory effects of arterial hypotension induced by adenosine. J Neurosurg 1983;58:69–76.
31. Johnson DJ, Muhlbacher F, Wilmore DW. Current Research Review: measurement of hepatic blood flow. J Surg Res 1985;39:470–81.
32. Lagerkranser M, Sollevi A, Irestedt L, Tidgren B, Andreen M. Renin release during controlled hypotension with sodium nitroprusside, nitroglycerin and adenosine: a comparative study in the dog. Acta Anaesthesiol Scand 1985;29:45–9.

Low-Dose Enflurane as Adjunct to High-Dose Fentanyl in Patients Undergoing Coronary Artery Surgery:

Stable Hemodynamics and Maintained Myocardial Oxygen Balance

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HEIKKILÄ H, JALONEN J, AROLA M, HOVI-VIANDER M, LAAKSONEN V. Low-dose enflurane as adjunct to high-dose fentanyl in patients undergoing coronary artery surgery: stable hemodynamics and maintained myocardial oxygen balance. Anesth Analg 1987;66:111–6.

The effects of enflurane (end-tidal concentration 0.7%) on central and coronary hemodynamics and myocardial oxygenation were studied during steady state, high-dose fentanyl anesthesia in ten patients undergoing coronary artery bypass grafting operations. Compared with the response in ten patients receiving the same fentanyl anesthesia (100 μg/kg) without enflurane supplementation, enflurane caused a moderate reduction in mean arterial pressure, systemic vascular resistance, and left ventricular stroke work index. No patient showed signs of myocardial ischemia, and mean coronary sinus flow and calculated coronary resistance remained unchanged. Surgical stimulation induced no central or coronary hemodynamic responses in the enflurane–fentanyl group. No coronary hemodynamic changes occurred in the fentanyl group, but a marked increase in arterial pressure and systemic vascular resistance was seen. Myocardial oxygen extraction decreased in the enflurane supplemented group although it increased in the fentanyl group after surgical stimulation. Three fentanyl group patients and one enflurane–fentanyl group patient had a low myocardial lactate extraction as a sign of myocardial ischemia during surgery. We conclude that a 0.7% enflurane supplementation of 100 μg/kg fentanyl anesthesia does not endanger myocardial oxygenation and effectively prevents central and coronary hemodynamic responses to skin incision and sternotomy in patients undergoing coronary artery surgery.

Key Words: ANESTHESIA—cardiovascular. ANESTHETICS, INTRAVENOUS—fentanyl. ANESTHETICS, VOLATILE—enflurane.

Preservation of hemodynamic stability and myocardial oxygenation is usually established during anesthetic induction and tracheal intubation in most patients undergoing a coronary artery bypass operation with high-dose fentanyl anesthesia (1,2). However, during sternotomy a hypertensive response is often seen in spite of total doses of 50–100 μg/kg of fentanyl (1,3). Because increasing the total doses of fentanyl (4,5) or different modifications of the technique for administering fentanyl (6) have not been satisfactory in preventing this response, inhalation anesthetics (4) and vasodilating drugs (4,7) are usually used as adjuvants to high-dose fentanyl anesthesia during sternotomy. However, the coronary hemodynamic effects of these agents are not fully understood and unfavorable regional changes in the myocardial oxygenation have been reported during anesthesia with near-MAC concentrations of enflurane in patients with ischemic heart disease (8,9). In this study we examined the central and coronary hemodynamic effects of enflurane when used as a low-concentration adjuvant to high-dose fentanyl anesthesia in order to prevent hypertension during the sternotomy in patients undergoing coronary bypass grafting.

Patients and Methods

After obtaining their informed consent, twenty patients scheduled for elective coronary bypass grafting were studied. The study protocol was also approved by the Ethics Committee of the Medical Faculty of the University of Turku. No patient had a left ventricular ejection fraction below 0.45 or a coexisting valvular

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Supported in part by a research grant from The Academy of Finland.

Received from the Department of Anesthesiology, Turku University Central Hospital, Turku, Finland. Accepted for publication September 3, 1986.

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Table 1. Patient Data

	F	E + F
Age (years)*	58 ± 3	52 ± 5
Sex (male/female)	10/0	10/0
Diseased main coronaries* (number of vessels)	2.5 ± 0.5	2.6 ± 0.4
LV ejection fraction (%)*	71 ± 11	65 ± 15
LV wall dyskinesia (number of patients)	3	5
LV end-diastolic pressure*	12 ± 7	16 ± 6
AMI history (number of patients)	6	6
Arterial hypertension (number of patients)	3	1
NYHA class (number of patients)		
II	1	2
III	9	8

Abbreviations: F, fentanyl group; E+F, enflurane-supplemented fentanyl group; LV, left ventricle; AMI, acute myocardial infarction.

*Mean values ± SD are presented.

anomaly. Preoperative patient characteristics are summarized in Table 1. All medications except β-blockers were discontinued the evening before the surgery; the last oral dose of β-blocker (metoprolol) was given to the patients 1.5 hr before induction of anesthesia. Premedication consisted of 0.2 mg/kg morphine and 6 μg/kg scopolamine given intramuscularly 1 hr before induction. A triple lumen, flow-directed, pulmonary artery thermodilution catheter and a Webster coronary sinus catheter were inserted under fluoroscopy, and a radial artery was cannulated using local anesthesia.

Anesthesia induction and maintenance were similar in all patients until the beginning of the operation. Anesthesia was induced with an intravenous infusion of 75 μg/kg of fentanyl preceded by an injection of 4 mg (patients with less than 80 kg of body weight) or 5 mg (patients over 80 kg) of lorazepam and, for muscle relaxation, 1.5 mg of pancuronium. Additional pancuronium up to a total dose of 0.1 mg/kg was injected when the patient became unresponsive to verbal commands. After tracheal intubation the patients were ventilated with oxygen in air (F_{IO_2} 0.40). For anesthetic management during the operation the patients were randomly divided into two groups, a fentanyl group and an enflurane–fentanyl group. Before the skin incision a 25-μg/kg dose of fentanyl was given to the patients in both groups. In the enflurane–fentanyl group, enflurane was administered to reach a stable end-tidal concentration of 0.7% (Normac, Datex, Espoo, Finland) before the start of surgery. Normoventilation was assured by measurements of end-tidal CO_2 tensions (Normocap, Datex, Espoo, Finland).

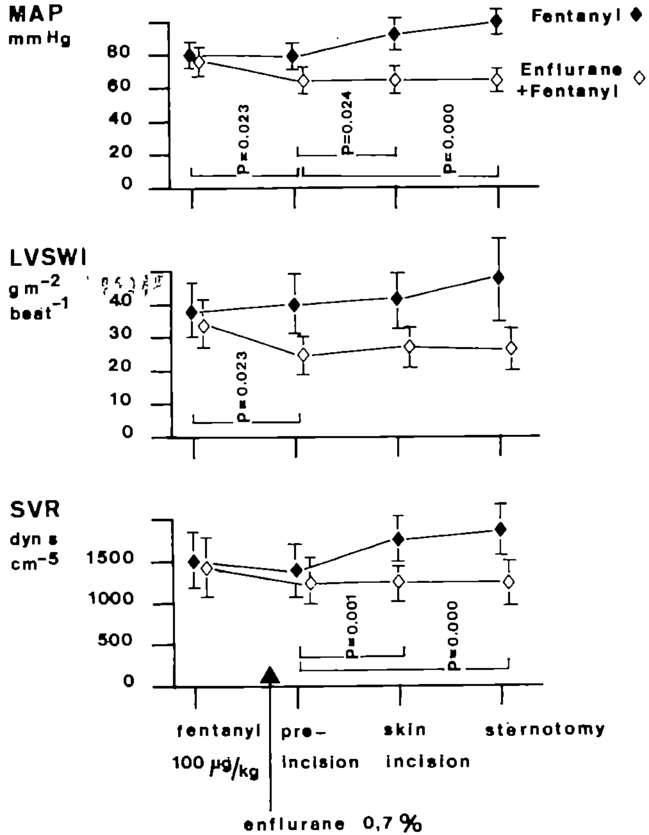

Figure 1. The effects of enflurane on central hemodynamics and on hemodynamic responses to surgery in patients undergoing coronary revascularization with high-dose fentanyl anesthesia. MAP, mean systemic arterial pressure; LVSWI, left ventricular stroke work index; SVR, systemic vascular resistance. P denotes the error risk in considering enflurane to have an effect on the response between the measuring occasions indicated, as compared with the group without enflurane.

Baseline hemodynamic and cardiometabolic data were recorded about 30 min after induction after preparation of the patient for surgery. At this stage patients had received the total dose of 100 μg/kg of fentanyl. The cardiac index, determined by thermodilution, and systemic arterial, pulmonary arterial, pulmonary capillary wedge, and central venous pressures at end expiration were recorded. Heart rate and ECG from six standard extremity leads and chest lead V_5 were recorded and coronary sinus flow was measured using the retrograde thermodilution method described by Ganz et al. (10). An ST-segment change of 0.1 mV or more or a decrease in myocardial lactate extraction of at least 50% and to a value less than 15% were taken as signs of myocardial ischemia. The latter criteria are based on pacing-induced angina studies in awake patients with coronary artery disease conducted by Ihlen et al. (11). Coronary vascular resistance was calculated using the formula (diastolic ar-

Table 2. Changes in Central Hemodynamic Parameters

	Group	1 Before enflurane	2 After enflurane	3 After skin incision	4 After sternotomy	Group–event interaction, error risk Overall	1 vs 2	2 vs 3	2 vs 4
MAP (mm Hg)	F	115 ± 12	112 ± 9	129 ± 12	141 ± 13	0.000	0.023	0.024	0.003
	E+F	108 ± 11	90 ± 9	92 ± 7	90 ± 10	—	—	—	—
PCWP (mm Hg)	F	6 ± 2	6 ± 2	7 ± 3	6 ± 4	—	—	—	—
	E+F	8 ± 2	9 ± 2	10 ± 3	9 ± 3	—	—	—	—
HR (beats/min)	F	59 ± 12	59 ± 10	58 ± 10	59 ± 10	—	—	—	—
	E+F	59 ± 11	58 ± 10	55 ± 10	58 ± 10	—	—	—	—
CI ($L \cdot min^{-1} \cdot m^{-2}$)	F	2.14 ± 0.53	2.28 ± 0.49	2.02 ± 0.22	2.18 ± 0.34	—	—	—	—
	E+F	2.03 ± 0.42	1.92 ± 0.55	1.94 ± 0.43	1.93 ± 0.40	—	—	—	—
LVSWI ($g \cdot m/m^2$)	F	37.5 ± 8.8	39.8 ± 9.0	41.8 ± 8.5	48.3 ± 12.9	0.000	0.023	—	—
	E+F	33.2 ± 6.5	25.5 ± 6.0	27.8 ± 6.1	26.0 ± 6.2	—	—	—	—
SVR ($dyne \cdot cm \cdot sec^{-5}$)	F	1509 ± 308	1387 ± 293	1768 ± 252	1829 ± 318	0.000	—	0.012	0.000
	E+F	1438 ± 355	1256 ± 247	1251 ± 238	1235 ± 257	—	—	—	—

Abbreviations: F, fentanyl group; E + F, enflurane supplemented fentanyl group; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; HR, heart rate; CI, cardiac index; LVSWI, left ventricular stroke work index; SVR, systemic vascular resistance.

Values are mean ± SD. Significant group-event interaction in the analysis of variance for repeated measurements was regarded as a different response between the two groups on the measurement occasions indicated.

terial pressure – pulmonary capillary wedge pressure)/(coronary sinus flow). For evaluation of myocardial oxygenation, samples of blood from the radial artery and the coronary sinus were drawn simultaneously for immediate analysis of oxygen and lactate concentrations. To evaluate the effects of enflurane supplementation the measurements and blood samplings were repeated after a stable end-tidal enflurane concentration of 0.7% had been achieved, the observed changes then being compared with data collected during the same period from patients receiving fentanyl only. The hemodynamic and cardiometabolic responses to surgical stimulation were assessed by measuring the above parameters after the skin incision and after retraction of the sternal edges, and comparing these values with those obtained immediately before skin incision.

Analysis of variance for repeated measurements technique (12) was employed first on the whole data, and, in the case of a significant main effect or interaction, further contrasts between individual measuring occasions were made using the same analysis of variance technique. The Bonferroni correction for multiple comparisons was applied. Intergroup differences in responses between two measurement occasions surrounding events like enflurane administration, skin incision, and sternotomy were of main interest, and thus attention in the statistical analysis was focused on the group–event interaction term. Enflurane was considered to have an effect if there was group–event interaction at the risk level of 0.05 or less.

Results

Effects of Enflurane Itself

The 0.7% end-tidal enflurane concentration decreased mean arterial pressure (17%) and left ventricular stroke work index (23%), as opposed to stable levels in the group receiving high-dose fentanyl anesthesia without supplementation (Fig. 1, Table 2). In individual patients the mean arterial pressure decrease varied between 29 and 0%; the lowest value was 60 mm Hg. No changes occurred in other central hemodynamic parameters in either group at this stage. Neither were there changes in either group in coronary sinus blood flow or in calculated coronary vascular resistance during this time. The arterial–coronary sinus oxygen content difference showed a tendency to decrease in response to the administration of enflurane that was not statistically significant (Fig. 2, Table 3). There were no overall changes in myocardial lactate metabolism in the groups, but in one patient lactate extraction increased from an ischemic level (7%) to a nonischemic level (16%) during the administration of enflurane. No patient showed ST-segment changes in the ECG indicative of ischemia during this time period.

Enflurane and the Response to Surgery

The skin incision and sternotomy caused an average increase of 23% in mean arterial pressure and systemic vascular resistance in the fentanyl group whereas no changes in these parameters were seen in the enflurane–fentanyl group (Fig. 1, Table 2). Mean arterial

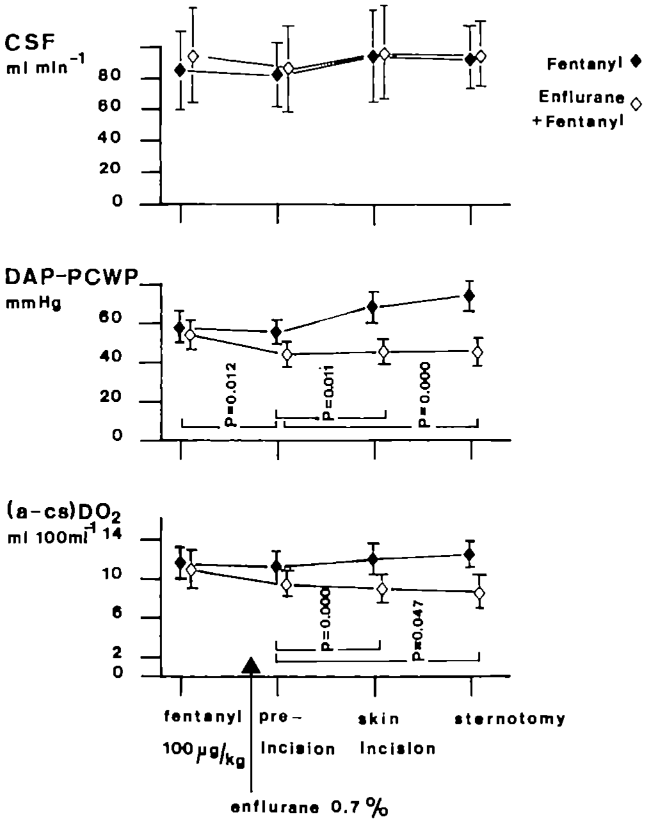

Figure 2. The effects of enflurane on coronary hemodynamics and myocardial metabolism and on responses to surgery in patients undergoing coronary revascularization with high-dose fentanyl anesthesia. CSF, coronary sinus blood flow; DAP-PCWP, diastolic systemic arterial pressure-pulmonary capillary wedge pressure (the difference was taken as the coronary perfusion pressure); (a-cs)DO$_2$, arterial-coronary sinus oxygen content difference. P as in figure 1.

pressure increased at least 20% in response to surgery in eight of ten fentanyl patients (the greatest increase was 45%), and an increase to a level at least 20% above awake, sedated levels was seen in three of ten fentanyl patients after sternotomy. In the enflurane–fentanyl patients mean arterial pressure changed little and remained lower than it was before induction in all patients.

After surgical stimulation the arterial–coronary sinus oxygen difference increased in the fentanyl group but decreased in the enflurane–fentanyl group (Fig. 2, Table 3). Surgery caused no significant change in either group in mean values of heart rate, cardiac index, coronary sinus flow, coronary vascular resistance, or myocardial lactate extraction. Coronary sinus blood flow did not change in either group despite a remarkable increase in the coronary perfusion pressure (diastolic arterial pressure − pulmonary capillary wedge pressure) in the fentanyl group in contrast to stable levels in the enflurane–fentanyl group (Fig. 2). However, myocardial lactate extraction decreased to a very low level—less than 10%—in one patient in each group. Additionally, two fentanyl patients had a sharp decrease (by 50 and 55%) in the myocardial lactate extraction during surgery; one of these two patients also had ischemic changes in lead V$_5$ in his ECG. In those fentanyl patients who showed ischemic signs during the surgical stimulation, a hypertensive response was also seen although no such response was noted in the single enflurane–fentanyl patient with a low level of myocardial lactate extraction (2%) during surgery.

Discussion

Evaluation of Methods

Chemical analysis of coronary sinus blood and the retrograde thermodilution flow measurement introduced by Ganz et al. do not measure regional changes in coronary flow and myocardial oxygenation; they reflect mainly changes in the whole left ventricular myocardium. Such data may thus tend to underestimate myocardial ischemia and must be interpreted with caution (13). Furthermore, limits for a "normal" myocardial lactate extraction remain undefined. We have used criteria of myocardial ischemia developed in the studies of Ihlen et al. (11), who found that pacing-induced angina in awake patients generally appeared in parallel with a reduction in myocardial lactate extraction by 50% or more and to an absolute value of 15% of the arterial lactate value. As angina is a late sign of myocardial ischemia, the lactate extraction criteria may also be somewhat insensitive. In our studies four patients fulfilled the lactate extraction criteria of myocardial ischemia, and two of these had simultaneous ECG evidence of ischemia.

Effects of Enflurane Itself

The supplementation of high-dose fentanyl anesthesia by 0.7% enflurane was well tolerated by all patients; only a moderate decrease in mean arterial pressure was seen in most patients, and no patient needed vasopressors or excessive volume loading to maintain arterial pressure. The work load of the left ventricle decreased after enflurane administration, and this decreased work load probably led to a decrease in myocardial oxygen extraction. In spite of the decrease in the coronary perfusion pressure no marked change was noted in the coronary sinus flow; this, together with the decreased arterial–coronary sinus

Table 3. Changes in Coronary Sinus Hemodynamics and Metabolism

	Group	1 Before enflurane	2 After enflurane	3 After skin incision	4 After sternotomy	Group–event interaction, error risk			
						Overall	1 vs 2	2 vs 3	2 vs 4
CPP (mm Hg)	F	58 ± 6	58 ± 5	68 ± 6	74 ± 6	0.000	0.011	0.012	0.000
	E + F	55 ± 8	45 ± 6	45 ± 5	45 ± 6	—	—	—	—
CSF (ml/min)	F	85 ± 33	81 ± 23	94 ± 5	92 ± 20	—	—	—	—
	E + F	96 ± 46	84 ± 36	95 ± 3[illegible]	93 ± 27	—	—	—	—
CVR (mm Hg·min/min)	F	0.83 ± 0.28	0.82 ± 0.23	0.88 ± 0.34	0.83 ± 0.20	—	—	—	—
	E + F	0.67 ± 0.26	0.63 ± 0.27	0.51 ± 0.14	0.52 ± 0.17	—	—	—	—
(a-cs)DO_2 (ml/dl)	F	11.6 ± 1.5	11.3 ± 1.5	11.9 ± 1.6	12.2 ± 1.3	0.000	(0.070)	0.000	0.047
	E + F	10.9 ± 1.8	9.8 ± 1.4	9.1 ± 1.3	8.6 ± 1.5	—	—	—	—
$MExtrO_2$ (%)	F	62 ± 5	62 ± 5	64 ± 5	66 ± 3	0.005	—	0.003	—
	E + F	61 ± 9	59 ± 7	57 ± 8	55 ± 11	—	—	—	—
MV_{O_2} (ml/min)	F	9.9 ± 4.3	9.1 ± 2.8	11.5 ± 7.6	11.3 ± 2.4	—	—	—	—
	E + F	10.4 ± 5.2	8.2 ± 3.9	8.8 ± 3.1	7.9 ± 2.4	—	—	—	—
MExtrLact (%)	F	35 ± 9	34 ± 10	34 ± 1[illegible]	36 ± 11	—	—	—	—
	E + F	26 ± 9	29 ± 8	24 ± 1[illegible]	25 ± 6	—	—	—	—

Abbreviations: F, fentanyl group; E + F, enflurane supplemented fentanyl group; CPP, coronary perfusion pressure; CSF, coronary sinus blood flow; CVR, coronary vascular resistance; (a-cs)DO_2, arterial-coronary sinus oxygen content difference; $MExtrO_2$, myocardial extraction of oxygen; MV_{O_2}, myocardial oxygen consumption; MExtrLact, myocardial extraction of lactate.

Values are mean ± SD. Significant group-event interaction in the analysis of variance for repeated measurements was regarded as a different response between the two groups on the measurement occasions indicated.

blood oxygen content difference, could speak for a coronary vasodilatory action of enflurane, though the change in the calculated vascular resistance was not statistically significant. The findings of this study concerning hemodynamic responses to enflurane are in agreement with previous findings (1,14), although we observed no change in the pulmonary capillary wedge pressure or in coronary hemodynamics, probably because the concentration of enflurane was so low.

Animal experiments have demonstrated that the main favorable effect of an anesthetic on the ischemic myocardium is a decrease in left ventricular oxygen demand due to decreased work load and/or a decrease in heart rate (15,16). We did not see any signs of myocardial ischemia that could be accounted for by the addition of enflurane and which could be detected with the methods used in this study. In most of our enflurane–fentanyl patients the myocardial lactate extraction increased when enflurane was added to the fentanyl anesthesia and thus myocardial ischemia is not probable, although regional ischemia cannot be excluded. In one patient the probable ischemia (low myocardial lactate extraction) present during the baseline measurements was relieved to some extent, probably because of the decrease in heart rate from 77 to 64 beats/min and a decrease in mean arterial pressure from 85 to 60 mm Hg, associated with a slight increase in coronary sinus flow and a 50% decrease in calculated coronary vascular resistance. These findings speak against an unfavorable coronary blood flow redistribution or coronary steal.

Enflurane and the Response to Surgery

There is little information about the optimal concentration of enflurane for supplementing high-dose fentanyl anesthesia during the surgical stimulation phase in patients undergoing coronary artery surgery. The concentration of enflurane used in this study was based partly on pilot studies and partly on data from the animal experiments of Murphy and Hug (17) in which large doses of fentanyl decreased the MAC of enflurane in the dog by 60–70%. In the present study an end-tidal concentration of 0.7% of enflurane in association with 100 μg of fentanyl prevented hemodynamic response to surgical stimulation in 60% of the patients and this concentration can thus be considered to be near the MAC of enflurane under these conditions. The enflurane concentration used was also sufficient to maintain mean arterial pressure during sternotomy below the level preceding induction in all patients, which indicates good hemodynamic stability. Despite this stability one of the enflurane-supplemented patients developed myocardial ischemia during surgery, emphasizing the fact that absence of central hemodynamic changes does not necessarily exclude myocardial ischemia, as stated before (1). On the other hand, the three fentanyl group patients that developed myocardial ischemia had associated marked hemodynamic stimulation, in turn emphasizing that marked hemodynamic stimulation in a patient having coronary artery disease carries a considerable risk of associated myocardial ischemia.

Would, then, higher concentrations of enflurane, supplemented with ordinary doses of fentanyl, be more effective in protecting patients from hemodynamic stimulation and myocardial ischemia? In a previous study we gave anesthesia with enflurane as the main anesthetic (inspired concentrations varying from 1.5% to 3% at different stages of the procedure), supplemented with conventional doses (7.5 μg/kg) of fentanyl to patients undergoing coronary surgery (1). We found that it was often not possible to reach a concentration of enflurane that would prevent hemodynamic responses to skin incision and sternotomy without causing a severe decrease in mean arterial pressure (1). Moffit et al. (18) gave enflurane in order to maintain the mean arterial pressure below the awake level together with a fentanyl dose of 30 μg/kg. The average enflurane concentration needed was 1.6%. Moffit et al. observed a slight increase in systemic and coronary vascular resistances and a decrease in the coronary sinus flow during sternotomy, although no signs of myocardial ischemia were seen. Tarnow et al. found that a low concentration (0.5% end-tidal) of isoflurane—which perhaps is a more powerful coronary vasodilator than enflurane—given together with nitrous oxide, was able to improve the tolerance to pacing-induced myocardial ischemia (19). On the basis of the experience of these studies it seems to us that the use of a high dose of fentanyl (100 μg/kg) as the basic anesthesia provides hemodynamic stability during induction and that this high-dose fentanyl anesthesia can be easily supplemented with a fairly low concentration of enflurane during the stress periods in such a way that hemodynamic responses to sternotomy can be prevented.

In conclusion, supplementation of high-dose fentanyl anesthesia (100 μg/kg) with a low concentration of enflurane during surgery in patients undergoing coronary artery procedures caused only moderate hemodynamic depression without endangering myocardial oxygenation. Compared with patients receiving the same fentanyl anesthesia without enflurane, hemodynamic stability was observed in enflurane–fentanyl patients during skin incision and sternotomy. The hemodynamic stability during enflurane–fentanyl anesthesia did not, however, prevent the development of myocardial ischemia in one patient during surgery.

References

1. Heikkilä H, Jalonen J, Arola M, Laaksonen V. Haemodynamics and myocardial oxygenation during anaesthesia for coronary artery surgery: comparison between enflurane and high-dose fentanyl anaesthesia. Acta Anaesthesiol Scand 1985;29:457–64.
2. Quintin L, Whalley DG, Wynands JE, Morin JE, Burke J. High dose fentanyl anaesthesia with oxygen for aorto-coronary bypass surgery. Can Anaesth Soc J 1981;28:314–20.
3. Sonntag H, Larsen R, Hilfiker O, Kettler D, Brockschnieder B. Myocardial blood flow and oxygen consumption during high-dose fentanyl anesthesia in patients with coronary artery disease. Anesthesiology 1982;56:417–22.
4. Wynands JE, Townsend GE, Wong P, Whalley DG, Srikant CB, Patel YC. Blood pressure response and plasma fentanyl concentrations during high- and very high-dose fentanyl anesthesia for coronary artery surgery. Anesth Analg 1983;62:661–5.
5. Wynands JE, Wong P, Townsend GE, Sprigge JS, Whalley DG. Narcotic requirements for intravenous anesthesia. Anesth Analg 1984;63:101–5.
6. Bovill JG, Sebel PS, Stanley TH. Opioid analgesics in anesthesia: with special reference to their use in cardiovascular anesthesia. Review. Anesthesiology 1984;61:731–55.
7. Heikkilä H, Jalonen J, Arola M, Laaksonen V. Surgical stimulation during high-dose fentanyl anaesthesia: effects of dehydrobenzperidol on the haemodynamics and myocardial oxygenation. Acta Anaesthesiol Scand 1985;29:259–64.
8. Reiz S. Effects of enflurane–nitrous oxide anaesthesia and surgical stimulation on regional coronary haemodynamics in a patient with LAD bypass graft. Acta Anaesthesiol Scand 1983;27:417–20.
9. Reiz S, Bålfors E, Sörensen MB, Häggmark S, Nyhman H. Coronary haemodynamic effects of general anesthesia and surgery. Modification by epidural analgesia in patients with ischemic heart disease. Regional Anesth 1982;7(suppl):S8–S18.
10. Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow by continuous thermodilution in man. Circulation 1971;44:181–95.
11. Ihlen H, Simonsen S, Vatne K. Reproducibility of ischaemic lactate metabolism during atrial pacing in man. Cardiology 1983;70:177–83.
12. Davidson M, Toporek J. General univariate and multivariate analysis of variance and covariance, including repeated measures. In: Dixon WJ, ed. BMDP statistical software 1981. Berkeley: University of California Press, 1981:388–412.
13. Apstein CS, Gravino F, Hood WB, Jr. Limitations of lactate production as an index of myocardial ischemia. Circulation 1979;60:877–88.
14. Moffit EA, Imrie DD, Scovil JE, et al. Myocardial metabolism and haemodynamic responses with enflurane anaesthesia for coronary artery surgery. Can Anaesth Soc J 1984;31:604–10.
15. Merin RG, Verdouw PD, deJong JW. Myocardial functional and metabolic responses to ischemia in swine during halothane and fentanyl anesthesia. Anesthesiology 1982;56:84–92.
16. van der Vusse GJ, van Belle H, van Gerven W, Kruger R, Reneman RS. Acute effect of fentanyl on haemodynamics and myocardial carbohydrate utilization and phosphate release during ischaemia. Br J Anaesth 1979;51:927–35.
17. Murphy MR, Hug CC, Jr. The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. Anesthesiology 1982;57:485–8.
18. Moffit EA, McIntyre AJ, Barker RA, et al. Myocardial metabolism and hemodynamic responses with fentanyl–enflurane anesthesia for coronary arterial surgery. Anesth Analg 1986;65:46–52.
19. Tarnow J, Markschies-Hornung A, Schulte-Sasse U. Isoflurane improves the tolerance to pacing-induced myocardial ischaemia. Anesthesiology 1986;64:147–56.

The Neuromuscular Blocking Effect of Vecuronium on the Human Diaphragm

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CHAUVIN M, LEBRAULT C, DUVALDESTIN P. The neuromuscular blocking effect of vecuronium on the human diaphragm. Anesth Analg 1987;66:117–22.

This study compares the neuromuscular blocking effect of vecuronium (0.1 mg/kg) on the diaphragm and the adductor pollicis in nine anesthetized patients. Monitoring of the diaphragm consisted of measurement of the transdiaphragmatic pressure after bilateral phrenic nerve stimulation. Onset time for neuromuscular blockade of the diaphragm was 1.6 ± 0.3 min (± SD) compared to 2.5 ± 0.3 min in the adductor pollicis ($P < 0.001$). The diaphragm recovered earlier and more rapidly than the adductor pollicis. The twitch height (TH) returned to 25% of its control value after 27 ± 8 min for the diaphragm, compared to 41 ± 11 min for the adductor pollicis ($P < 0.01$). Complete TH recovery was achieved after 49 ± 14 min for the diaphragm and after 74 ± 22 min for the adductor pollicis ($P < 0.01$). The recovery index of 12 ± 4 min for the diaphragm was significantly shorter ($P < 0.05$) than for the adductor pollicis (20 ± 9 min.) We conclude that monitoring of peripheral muscles in anesthetized patients given vecuronium provides adequate information about the degree of paralysis of the diaphragm.

Key Words: NEUROMUSCULAR RELAXANTS—vecuronium.

The evaluation of the neuromuscular blocking effect of muscle relaxants usually consists of measuring the evoked muscle response after supramaximal nerve stimulation. Monitoring of peripheral muscles that are easily accessible to nerve stimulation and evaluation of their electrical or mechanical responses has been used to quantify the effect of muscle relaxants in humans (1). However, a major effect of muscle relaxants is profound paralysis of respiratory muscles. Satisfactory intubating conditions require complete paralysis of the vocal cords, diaphragm and abdominal wall musculature. Furthermore, paralysis of the diaphragm and of abdominal muscles, which are an integral part of respiratory function, is important during abdominal surgery.

The effect of several muscle relaxants on the hand grip test and the vital capacity in unanesthetized volunteers was studied by Foldes et al. (2), who observed a sparing effect of depolarizing and nondepolarizing relaxants on respiratory muscles. Further confirmation of the respiratory effect of *d*-tubocurarine was provided by Wymore and Eisele (3) who showed that in anesthetized patients more *d*-tubocurarine was required to abolish inspiratory pressure generated during spontaneous breathing than was required to abolish the thumb twitch. In unanesthetized volunteers it was shown that when *d*-tubocurarine almost abolished the hand grip strength, the slope of the CO_2 response curve remained unchanged and vital capacity decreased only 48% (4–6), further confirming the respiratory sparing effect of *d*-tubocurarine.

The direct effect of muscle relaxants on the neuromuscular junction is quantitated by measuring the evoked mechanical or electrical response to supramaximal motor nerve stimulation. In this respect, the effect of muscle relaxants on the diaphragm was only studied in animals. More *d*-tubocurarine was required to block neuromuscular transmission in the diaphragm than in the peripheral muscles and the diaphragm recovered sooner than peripheral muscles in the cat and the dog (7). The resistance of the diaphragm to muscle relaxants was explained by a greater margin of safety in its neuromuscular transmission (7). The diaphragm can function with only one tenth of the receptor pool available, whereas in most peripheral muscles one fifth of the receptors available is necessary to obtain a normal twitch response (7).

Supported by the Faculté de Médecine Paris Ouest and Association des Myopathes de France. Presented at the 1985 Annual Meeting of the American Society of Anesthesiologists, San Francisco, California.

Received from the Department of Anesthesia, Hôpital Ambroise Paré, Université Paris 5, Boulogne sur Seine, France. Accepted for publication September 8, 1986.

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Table 1. Characteristics of the Patients

Patient number	Body weight (kg)	Age (yr)	Sex	Surgical procedure
1	60	45	F	Breast surgery
2	76	48	M	Variceal stripping
3	73	39	M	Aorto bifemoral bypass
4	71	80	M	Abdominal hernia
5	54	62	M	Herniorraphy
6	72	49	M	Herniorraphy
7	65	60	M	Herniorraphy
8	53	48	F	Variceal stripping
9	57	50	M	Herniorraphy

The aim of the present study was to compare the effect of an intubating dose of vecuronium on the neuromuscular functions of the diaphragm and of the adductor pollicis in anesthetized patients.

Methods

Patients

Nine ASA Class I or II patients scheduled for elective herniorraphy or extremity surgery, were studied. The characteristics of the patients are listed in Table 1. The patients ranged in age from 39 to 80 yr (53.4 ± 7.5 yr, mean ± SD) and weighed 53–76 kg (64.6 ± 8.8 kg). Each patient gave informed consent for the study, which was approved by the Committee for Human Research of Paris Ouest medical Faculty.

Premedication consisted of lorazepam, 2.5 mg given orally 2 hr before anesthesia. Anesthesia was induced with thiopental, 6–8 mg/kg, and fentanyl, 2 μg/kg, intravenously. Tracheal intubation was performed under topical anesthesia with 2% lidocaine. Anesthesia was maintained with nitrous oxide (60% in oxygen) delivered by controlled ventilation and repeated doses of fentanyl (total dose 0.2–0.7 mg) and thiopental (total dose 400–700 mg). Ventilation was adjusted to maintain end-tidal CO_2 at 5% (Datascope 500 CO_2 analyzer). Esophageal and palmar temperatures were measured during the study. A single intravenous bolus dose (10 sec) of vecuronium, 0.1 mg/kg, was administered approximately 20 min after induction of anesthesia after monitoring devices had been established. The duration of general anesthesia was 94 ± 36 min.

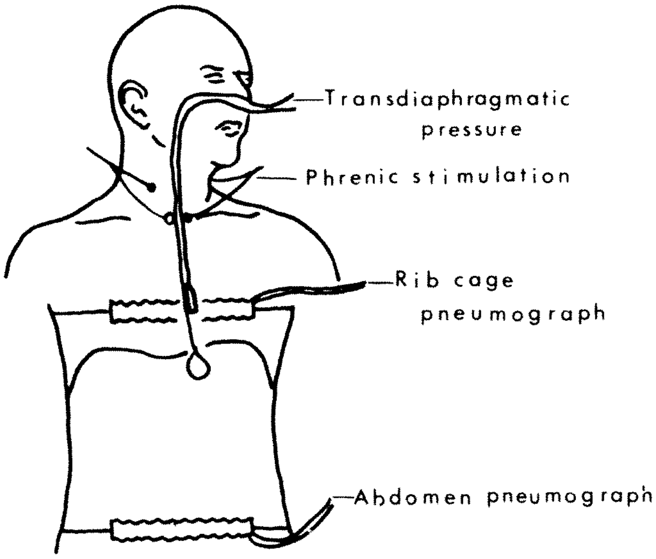

Figure 1. Monitoring of the neuromuscular blocking effect of vecuronium in anesthetized patients. Bilateral phrenic nerve stimulations were performed by using nerve needle electrodes at the neck. The strength of the diaphragm was measured by recording the transdiaphragmatic pressure (Pdi). The configuration of the diaphragm was checked by measuring the circumference of the thorax and the abdomen with the aid of a bellows pneumograph.

Clinical Protocol

The effect of vecuronium on the diaphragm was monitored by measuring the transdiaphragmatic pressure elicited after supramaximal bilateral phrenic nerve stimulation (Fig. 1). The transdiaphragmatic pressure (Pdi), which is defined as the difference between gastric and esophageal pressure (Pga − Ppl), was measured by means of two thin-walled latex balloons (10 cm length); one balloon was positioned in the stomach and the other in the middle third of the esophagus. Correct location of the balloons was checked by registering the atrial activity transmitted by the esophageal balloon and the shape of the pressure in the gastric balloon during respiratory movements.

The two balloon catheters were connected to a differential pressure force transducer (Validyne MP-45). Phrenic nerve stimulation was performed using a (Grass S 88) stimulator and nerve needle electrodes (DISA 13 L 60). The electrodes were inserted near the lower edge of the sternocleidomastoid muscle (8). Supramaximal stimuli of 0.2 msec duration were applied every 10 sec. To determine the optimal conditions of stimulation, the electrode position was adjusted and the stimulus voltage was increased while the evoked Pdi was displayed on an oscilloscope and recorded. Maximal stimulation was achieved at 20–30 V. The voltage was then increased 10–20% to ensure that stimulation remained supramaximal. During the diaphragm study, the lungs were inflated manually between two phrenic nerve stimulations. A respiratory bellows pneumograph (model 108 pneumograph Hewlett-Packard) was used to ensure that the muscle fiber length of the diaphragm was constant through-

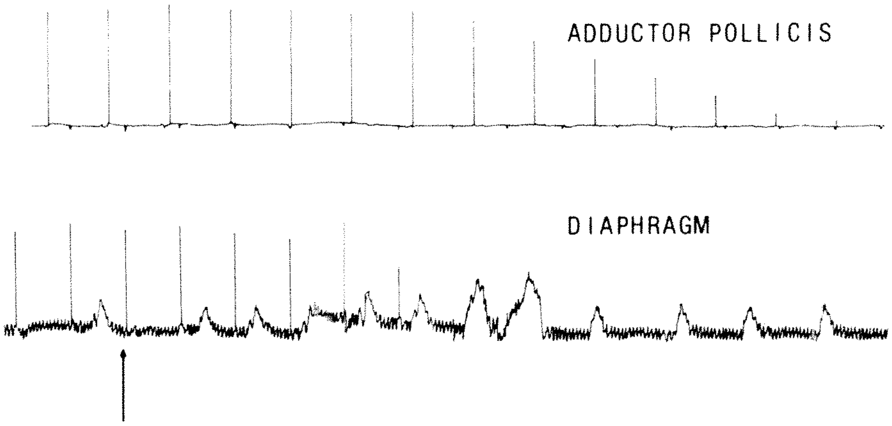

Figure 2. Simultaneous evolution of the twitch height of the diaphragm and of the adductor pollicis in one patient (patient 1) immediately after the administration of vecuronium (arrow). Supramaximal stimulations of the ulnar nerve and of the phrenic nerves were delivered every 10 sec. The onset time of vecuronium in the diaphragm and in the adductor pollicis were 1.1 and 2.1 min, respectively. Oscillations of the base line of diaphragm response estimated by the transdiaphragmatic pressure are due to the transmission of the atrial pressure and to ventilation.

Table 2. Neuromuscular Effect of 0.1 mg/kg Vecuronium on the Adductor Pollicis and the Diaphragm in Nine Anesthetized Patients

Patient number	Onset time (min)		TH10 (min)		TH25 (min)		TH50 (min)		TH75 (min)		TH100 (min)		TH25-75 (min)	
	A	D	A	D	A	D	A	D	A	D	A	D	A	D
1	2.1	1.1	29	14	28	15	32	18	38	19	46	27	10	4
2	3.0	1.8	43	21	50	25	63	28	78	36	97	51	28	11
3	2.4	1.6	26	17	29	21	33	27	38	34	49	39	9	13
4	2.8	1.7	36	30	39	33	47	43	57	52	76	59	18	19
5	2.2	1.4	44	25	55	28	69	32	86	38	98	49	31	10
6	2.3	2.2	42	38	46	41	54	48	76	56	89	71	30	15
7	2.3	2.0	46	30	55	32	68	39	82	45	98	64	27	13
8	1.8	1.5	30	23	35	25	40	28	48	35	59	37	13	8
9	2.3	1.3	29	21	33	23	40	26	45	35	56	50	12	12
Mean	2.5	1.6	36	24	41	27	50	32	61	39	74	49	20	12
± SD	± 0.3	± 0.3[a]	± 8	± 7[a]	± 11	± 8[b]	± 15	± 9[c]	± 20	± 11[b]	± 22	± 14[b]	± 9	± 4[c]

Abbreviations: A, adductor pollicis; D, diaphragm; TH10, TH25, TH50, TH75, and TH100, twitch height recovery time to 10, 25, 50, 75, and 100% of control value, respectively; TH25-75, time from 25 to 75% of recovery of control twitch tension.

[a] $P < 0.001$ vs adductor pollicis.

[b] $P < 0.01$ vs adductor pollicis.

[c] $P < 0.05$ vs adductor pollicis.

out the study. This instrument consists of two air-filled rubber bellows, 15 cm long and 1 cm wide, fixed circumferentially around the chest and the abdomen by nonelastic cords. Stretching of the bellows produces changes in air pressure, which are measured by a pressure transducer via a polythene tubing (Validyne DP-45). Neuromuscular function of the adductor pollicis was monitored simultaneously. The ulnar nerve was stimulated (Grass S 88®) at the wrist through surface electrodes by supramaximal impulses of 0.2 msec at 0.1 Hz. The elicited twitch tension of the adductor pollicis muscle was quantitated by a force transducer (Statham UC3).

After establishing a stable control response, a single bolus dose of vecuronium, 0.1 mg/kg, was administered and the following parameters were measured: time from injection to peak effect (onset time), time from injection to 10, 25, 50, 75, and 100% recovery (TH10, TH25, TH50, TH75, TH100) and time from 25 to 75% recovery of control twitch tension (TH25–75). Results are presented as means ± SD. Statistical comparisons were made using Student's paired *t*-test.

Results

Vecuronium, 0.1 mg/kg, induced 100% paralysis of both the diaphragm and the adductor pollicis in all patients. The onset time was always more rapid in the diaphragm than in the adductor pollicis. The simultaneous evolution of the onset of both diaphragmatic and adductor pollicis paralysis registered in a patient after the administration of vecuronium is shown in Figure 2. Recovery from paralysis occurred earlier in the diaphragm than in the adductor pollicis in all patients (Table 2). TH10 occurred after 24 ± 7 min in the diaphragm and after 36 ± 8 min in the adductor

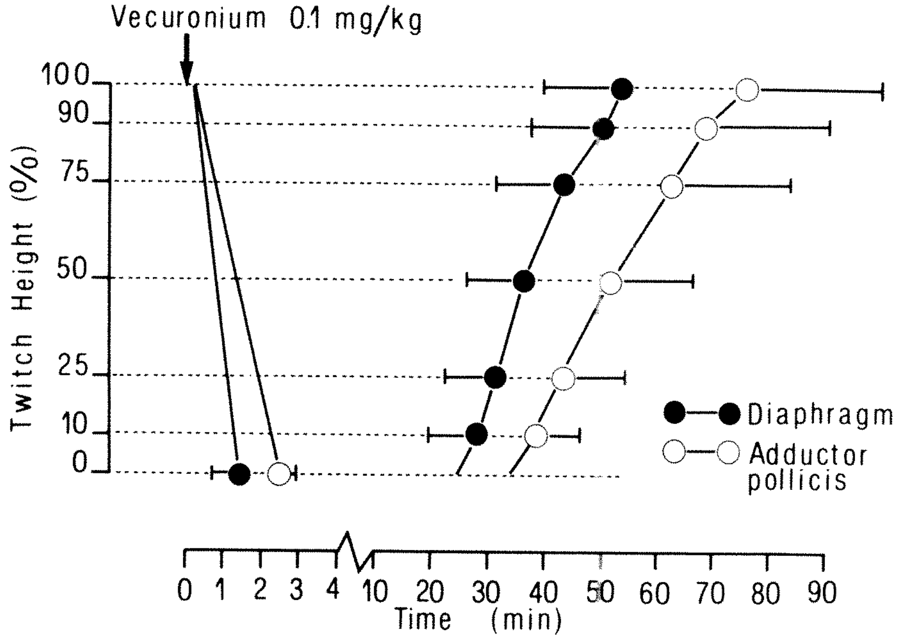

Figure 3. Simultaneous evolution of the neuromuscular blocking effect of vecuronium (0.1 mg/kg) in the diaphragm (white circles) and the adductor pollicis (black circles) in anesthetized patients.

pollicis ($P < 0.001$). Similarly, recovery times to 25, 50, 75 and 100% of the twitch height were significantly shorter in the diaphragm. When the diaphragm had completely recovered from paralysis, the TH of the adductor pollicis was still 50% (Fig. 3). The recovery index after vecuronium administration was 12 ± 4 min for the diaphragm, a value significantly less ($P < 0.05$) than that observed for the adductor pollicis (20 ± 9 min). The circumferences of the thorax and of the abdomen were not altered after the administration of vecuronium and remained unaltered until recovery from paralysis was complete. The mean esophageal and palmar temperatures were 35.3°C and 34.3°C at the start of the study and declined respectively to 34.9°C and 33.5°C at the end of the study.

Discussion

This study demonstrates that it is possible in anesthetized patients to monitor the neuromuscular function of the human diaphragm in the same manner as that of peripheral muscles. The Pdi is a valid index of the strength of the diaphragm provided that the length of its muscle fibers does not vary during the study (9). To ensure that the resting length of the diaphragm was the same before and after the administration of vecuronium, the circumferences of the rib cage and the abdomen were continuously monitored throughout the study. In each patient, the thoracic and abdominal circumferences were unchanged after the administration of a completely paralyzing dose of vecuronium, suggesting that the length of diaphragmatic muscle fibers also remained unchanged. It has been previously shown that general anesthesia causes a diminution in functional residual capacity (FRC) because of the cephalad shift of the diaphragm, but that the subsequent administration of muscle relaxants in anesthetized patients does not cause any further decrease in FRC (10,11). In addition, lung insufflations were performed between two phrenic nerve stimulations so that these stimulations were delivered when the diaphragm was at its resting length. In these conditions, it would appear reasonable to compare the effect of muscle relaxant on the diaphragm to its effect on peripheral muscles.

The dose of 0.1 mg/kg of vecuronium, which is the dose recommended to facilitate tracheal intubation (12), caused complete paralysis of the diaphragm in all patients, thus confirming the adequacy of this dose. The onset time was more rapid in the diaphragm than in the adductor pollicis muscle. For a particular muscle, onset time is mainly dependent upon its local blood flow; the higher the blood flow, the more rapid the onset of effect (13). The difference in onset time between the diaphragm and the adductor pollicis may be due to differences in their blood flows or in their structures. The diaphragm, a well perfused muscle (14), has a blood flow that is probably greater than that to the adductor pollicis. The difference in the temperatures measured in the space surrounding these muscles, the temperature being higher in the diaphragm, may reflect the difference in their respective blood flows. The influence of the mechanical activity on the respective blood flows of these two muscles was probably negligible, because ventilation was controlled in this study and the two muscles were submitted to the same rate of supramaximal nerve stimulations and therefore to the same work. Another possibility is that the accessibility of muscle relaxant to the motor endplate is different due to differences in the structures of these muscles, both of which are composed predominantly of slow twitch fibers (15,16). The rapid onset time of vecuronium in respiratory muscles, compared to peripheral muscles, may provide an explanation for the relatively good intubating conditions obtained soon after the injection of the relaxant, despite the persistence of peripheral residual muscular tone. Theoretically, good intubating conditions are present when the peripheral TH decreased 95%. This condition is rarely observed before 2.5–4 min after vecuronium injection in the absence of inhaled halogenated agent, whereas tracheal intubation is often performed before the second min in many clinical trials with nondepolarizing relaxants (17,18). The difference between the onset time of peripheral paralysis and the intubating time can be explained by the more rapid onset of paralysis of laryngeal muscles and the diaphragm. The recovery of the diaphragm occurred earlier than recovery of the adductor pollicis and was complete when the peripheral twitch was still depressed 50%. This pattern of recovery has also been observed with *d*-tubocurarine in various animal species (7,19). These results further support the concept of diaphragmatic resistance to muscle relaxants (7) and are in accordance with the preliminary results of Donati et al. (20) who observed a greater than twofold difference between the diaphragm and the adductor pollicis with respect to their sensitivities to pancuronium in man.

The rapidity of recovery from paralysis, a relatively prolonged phenomena compared with the onset of paralysis, is influenced by two factors: the decrease in muscle relaxant concentration in the biophase and in the plasma (21) and the drug association constant for the receptor–relaxant complex. First, at a given time the concentration of vecuronium should be the same in the diaphragm as in the adductor pollicis. Thus the concentration of muscle relaxant corresponding to a given degree of paralysis will be greater in the diaphragm than in the adductor pollicis because the diaphragm recovers earlier from paralysis than the adductor pollicis. Second, one might expect that the dissociation constant of vecuronium is the same in the two muscles in man because the affinity of *d*-tubocurarine for the diaphragm is similar to that of other muscles (22). Therefore at any given similar degree of paralysis of these two muscles, there is probably a higher occupancy of postsynaptic receptors in the diaphragm than in the adductor. These results confirm the concept of a higher margin of safety of neuromuscular transmission in the diaphragm, which starts to recover when less than 90–95% of postsynaptic receptors are occupied (7). Another factor that might explain the difference in muscle response is the temperature difference between the muscles studied. Hypothermia is known to potentiate the action of nondepolarizing relaxants including vecuronium (23). However, the temperature of the adductor pollicis was only 1–1.5°C below that of the diaphragm throughout the study and it appears unlikely that such a small temperature difference will cause a large change in the response to vecuronium. The shorter recovery index of the diaphragm compared with that of the adductor pollicis after vecuronium may possibly be explained by the biexponential mode of decline of vecuronium plasma concentration. Because the rate of recovery from paralysis is influenced by the rate of decrease in plasma concentration of vecuronium, the faster the decrease in the concentration, the more rapid the recovery. Diaphragmatic recovery begins soon after the administration of 0.1 mg/kg of vecuronium, at which time the plasma concentration is mostly influenced by distribution processes, whereas during recovery of the adductor pollicis the plasma concentration decreases more slowly, because of the predominant influence of elimination processes.

The results of this study suggest that the monitoring of the neuromuscular function of peripheral muscles during the recovery from vecuronium-induced paralysis provides valuable information about the degree of paralysis of the diaphragm. After administration of vecuronium, when the adductor pollicis twitch has recovered to 100% of its control value it can be assumed that there is no further residual depression of the diaphragmatic twitch. In the present study only spontaneous recovery was considered, and it remains to be determined whether or not diaphragmatic recovery is more rapid than that of peripheral muscles after the administration of anticholinesterase inhibitors. It is also important to determine if the present results also apply to other respiratory muscles, particularly the laryngeal muscles, and whether the present results apply to other nondepolarizing relaxants.

References

1. Ali HH, Savarese JJ. Monitoring of neuromuscular function. Anesthesiology 1976;45:216–49.
2. Foldes FF, Monte AP, Brunn HM, Wolfson B. Studies with muscle relaxants in unanesthetized subjects. Anesthesiology 1961;22:230–6.

3. Wymore ML, Eisele JH. Differential effects of d-tubocurarine on inspiratory muscles and two peripheral muscle groups in anesthetized man. Anesthesiology 1978;48:360–2.
4. Gal TJ, Smith TC. Partial paralysis with *d*-tubocurarine and the ventilatory response to CO_2: an example of respiratory sparing? Anesthesiology 1976;45:22–8.
5. Gal TJ, Goldberg SK. Relationship between respiratory muscle strength and vital capacity during partial curarization in awake subjects. Anesthesiology 1981;54:141–7.
6. Gal TJ, Goldberg SK. Diaphragmatic function in healthy subjects during partial curarization. J Appl Physiol 1980;48:921–6.
7. Waud BE, Waud DR. The margin of safety of neuromuscular transmission in the muscle of the diaphragm. Anesthesiology 1972;37:417–22.
8. Aubier M, Murciano D, Lecocguic Y, Viires N, Pariente R. Bilateral phrenic stimulation: a simple technique to assess diaphragmatic fatigue in humans. J Appl Physiol 1985;58:58–64.
9. De Troyer A, Estenne M. Limitations of measurement of transdiaphragmatic pressure in detecting diaphramatic weakness. Thorax 1981;36:169–74.
10. Froese AB, Bryan AC. Effects of anesthesia and paralysis on diaphragmatic mechanics in man. Anesthesiology 1974;41:242–55.
11. Westbrook PR, Stubbs SE, Sessler AD, Rehder K, Hyatt RE. Effects of anesthesia and muscle paralysis on respiratory mechanics in normal man. J Appl Physiol 1973;34:81–6.
12. Fahey MR, Morris RB, Miller RD, Sohn YJ, Cronnelly R, Gencarelli P. Clinical pharmacology of ORG NC45 (Norcuron™): a new nondepolarizing muscle relaxant. Anesthesiology 1981;55:6–11.
13. Goat VA, Yeung ML, Blakeney C, Feldman SA. The effect of blood flow upon the activity of gallamine triethiodide. Br J Anaesth 1976;48:69–73.
14. Rochester DF, Briscoe AM. Metabolism of the working diaphragm. Am Rev Respir Dis 1979;119:101–6.
15. Rochester DF. The diaphragm: contractile properties and fatigue. J Clin Invest 1985;75:1397–1402.
16. Johnson MA, Polgar J, Weightman D, Appleton D. Data on the distribution of fibre types in thirty-six human muscles: an autopsy study. J Neurol Sci 1973;18:111–29.
17. Foldes FF, Nagashima H, Boros M, Tassonyi E, Fitzal S, Agoston S. Muscular relaxation with atracurium, vecuronium and duador under balanced anaesthesia. Br J Anaesth 1983;55:97S–103S.
18. Bencini A, Newton DEF. Rate of onset of good intubating conditions, respiratory depression and hand paralysis after vecuronium. Br J Anaesth 1984;56:959–65.
19. Tran DQ, Amaki Y, Ohta Y, Nagashima H, Duncalf D, Foldes FF. Simultaneous in vivo measurement of NM block on three muscles. Anesthesiology 1982;57:A276.
20. Donati F, Antzaka C, Bevan DR. The diaphragm and adductor pollicis dose-response curves for pancuronium. Anesthesiology 1985;63:A322.
21. Shanks CA, Somogyi AA, Triggs EJ. Dose–response and plasma concentration–response relationships of pancuronium in man. Anesthesiology 1979;51:111–8.
22. Lu T. Affinity of curare-like compounds and their potency in blocking neuromuscular transmission. J Pharmacol Exp Ther 1970;174:560–6.
23. Buzello W, Schluermann D, Schlinder M, Spillner G. Hypothermic cardiopulmonary bypass and neuromuscular blockade by pancuronium and vecuronium. Anesthesiology 1985;62:201–4.

Effect of Pregnancy on Bupivacaine-Induced Conduction Blockade in the Isolated Rabbit Vagus Nerve

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FLANAGAN HL, DATTA S, LAMBERT DH, GISSEN AJ, COVINO BG. Effect of pregnancy on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve. Anesth Analg 1987;66:123–6.

Bupivacaine-induced conduction blockade of A, B, and C fibers of the isolated vagus nerve was compared in fourteen pregnant and fourteen nonpregnant rabbits. After a control period in HEPES-Liley solution, the isolated nerves were exposed to bupivacaine concentrations of 0.1 mM to 1.0 mM. After 30 min exposure, the nerves were stimulated supramaximally and the percent reduction in amplitude of A, B, and C fiber compound action potentials was recorded. Linear regressions were fitted by the least squares method. The A fiber conduction blockade was consistently greater in the nerves from pregnant rabbits ($P < 0.001$). The slope of the C fiber dose–response curves was also significantly greater in nerves from pregnant rabbits ($P < 0.01$). The results indicate that the response of isolated nerves from pregnant animals to local anesthetic-induced conduction blockade differs from that of nerves from nonpregnant animals. However, it is not certain whether the difference is related simply to a more rapid diffusion and shorter onset of block or an enhanced sensitivity of the nerve membrane during pregnancy.

Key Words: ANESTHETICS, LOCAL—bupivacaine. ANESTHESIA—obstetric.

It has been demonstrated that the dose requirement for lumbar epidural analgesia is reduced by approximately 30% in parturients (1). The reason for this reduced dosage requirement for conduction blockade in pregnant patients has not been clearly established. Suggested mechanisms include the following: 1) distension of the epidural veins, reducing the size of the epidural space, thus increasing the spread of local anesthetics; 2) hormonal changes that may alter the susceptibility of the nerve membrane to local anesthetics; and 3) other biochemical changes that may alter nerve response to local anesthetics (2).

Previous studies have indicated that onset of conduction blockade is more rapid in the rabbit vagus nerve from pregnant animals than the vagus nerve from nonpregnant animals after exposure to 0.35 mM of bupivacaine (3). The purpose of the current investigation was to compare the response of isolated nerves from pregnant and nonpregnant animals to varying concentrations of bupivacaine in order to determine whether a differential dose–response relationship exists.

Materials and Methods

The rabbits used in this experiment were housed in the Harvard Medical School, NIH approved, animal care facility in accordance with the "Guide for the care and use of laboratory animals" (DHHS publication no. (NIH) 78-23 revised 1978). Animals were also treated in accordance with the Harvard Medical Area "Guidelines for animal care and use of laboratory animals" which were drafted during the course of this experiment.

Fourteen pregnant and 14 nonpregnant New Zealand white rabbits were used in this study (3.5–4.0 kg). Pregnant rabbits were in the fourth week of gestation. Pregnancy was verified by uterine exploration. Animals were anesthetized with intravenous thiamylal (1.5 mg/kg) before being sacrificed by intravenous air embolus. The vagus nerves were rapidly removed and stored at room temperature (22°C) in HEPES-Liley solution containing 136.8 mM NaCl, 5.0 mM KCl, 2.0 mM $CaCl_2$, 1.0 mM $MgCl_2$, and 11.0 mM dextrose buffered by the addition of 3.0 mM

This paper was presented in part at the 1984 Meeting of the American Society of Anesthesiologists, New Orleans, LA. This study was supported in part by NIH Biomedical Research Support Grant *2507RR05489-21.

Department of Anesthesia Research Laboratories, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Accepted for publication September 16, 1986.

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N-2-hydroxyethylpiperazine-N′-2-ethanesulfonic acid (HEPES). The pH was adjusted to 7.35–7.40 by the addition of 0.1N NaOH. The nerves were transferred to a stimulation chamber as previously described (4). The intact vagus nerves were stimulated using surface platinum electrodes with a Grass S46 stimulator and a Grass Stimulus Isolation Unit. The stimulation frequency was 0.5 Hz. Stimulus duration was 0.05 msec for A fibers, 0.1 msec for B fibers and 1.0 msec for C fibers. Stimulus intensities were adjusted to obtain the maximum compound action potential (AP) on a Tektroniks model 5113 storage oscilloscope. Stimulus amplitudes for A, B, and C fibers were generally 4.5 V, 11 V, and 28 V, respectively. The experiments were performed at room temperature (22°C). Measurements of the compound AP amplitude were made from photographs of the AP images displayed on the storage oscilloscope. The A, B, and C fibers were identified by their respective conduction velocities of 25–50 m/sec, 5–15 m/sec, and <1.0 m/sec. Nerves having an A fiber compound AP less than 1 mV or C fiber compound AP less than 0.2 mV were considered damaged and were not accepted for experimental study.

The nerves were bathed with HEPES-Liley solution during a 30-min stabilization period. After recording baseline action potentials, the nerves were continuously bathed with a single bupivacaine test concentration (range, 0.1–1.0 mM) for an additional 30 min before evaluating the degree of conduction blockade. After testing, the nerves were washed with bupivacaine-free HEPES-Liley solution to demonstrate recovery and to ensure that the observed conduction blockade was not secondary to nerve damage. In order to be included in the analysis, the nerve had to recover to 85% of control AP amplitude.

The various bupivacaine solutions were prepared in HEPES-Liley salt solution and infused into the bath chamber at a constant rate of 1 ml/min. At the end of this period, the peak compound action potentials of the A, B, and C fibers were recorded and then compared to their respective control values. Results were expressed in terms of percent reduction in AP amplitudes achieved at the end of the 30-min exposure to the bupivacaine solution. The data were plotted in a log linear fashion with the percent blockade (ordinate) against the log of (bupivacaine concentration (M) × 10^4) (abcissa). Linear regressions were determined via least squares analysis. Standard statistical methods were used to determine linearity of regression, coefficients of correlation, and the difference between slopes. Differences between parallel lines were determined by analysis of covariance (5). Statistical significance was assumed with P values less than 0.05. Blood samples for measurement of progesterone levels were collected from the inferior vena cava and assayed by a previously described technique (6).

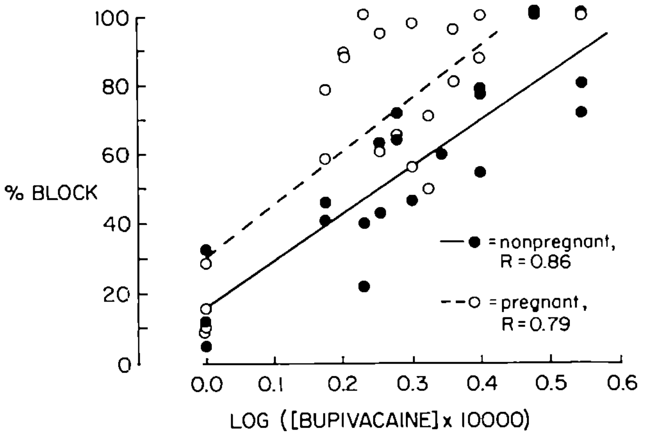

Figure 1. A Fibers. Log-linear plot illustrating the effect of pregnancy on the reduction of peak compound action potential amplitude of A fibers as a percent of control after 30 min exposure to different concentrations of bupivacaine. The linear regression equations for pregnant subjects was: percent block = $30.5^a + 153 \log$ (bupivacaine (M) × 10^4). The Cm = 0.134 mM. In nonpregnant subjects, the linear regression equation was: percent block = $16.1^a + 136 \log$ (bupivacaine (M) × 10^4). The Cm = 0.178 mM; Cm is the concentration of bupivacaine corresponding to 50% block. $^a P < 0.001$.

Results

The slopes of the linear regressions for A fibers in the absence of bupivacaine and in the presence of increasing concentrations (Fig. 1) were not significantly different (153 pregnant vs 136 nonpregnant). The correlation coefficients were 0.79 for pregnant and 0.86 for nonpregnant animals. Analysis of covariance revealed that these linear regressions represented significantly different parallel lines ($P < 0.001$), and therefore reduction in AP amplitude by a given concentration of bupivacaine was significantly greater in the pregnant group than in the nonpregnant group. The C fiber correlation coefficient was 0.91 in nerves from pregnant and 0.68 in nerves from nonpregnant animals. The slopes (132 pregnant vs 65 nonpregnant) of the C fiber linear regressions (Fig. 3) were significantly different ($P < 0.01$). Analysis of linear regressions for B fibers (Fig. 2) did not demonstrate significantly different slopes or parallelism. The minimum concentration necessary to produce 50% blockade (Cm) was calculated from the respective regressions. The results in each fiber group are listed in the respective figures.

Serum progesterone levels were measured in four pregnant (mean, 5.5 ng/ml) and nine nonpregnant rabbits (mean = 1.67 ng/ml). Comparison of the means

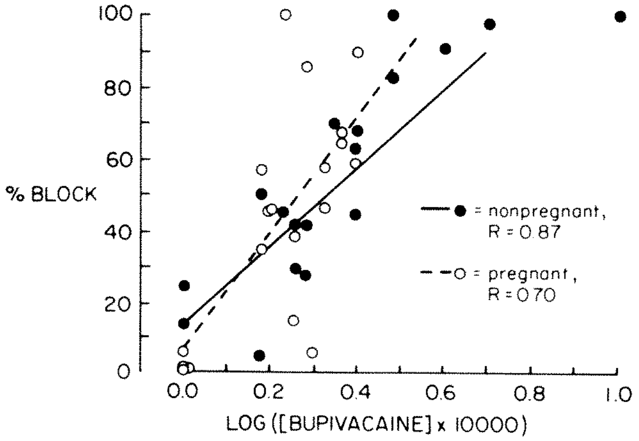

Figure 2. B Fibers. Log-linear plot illustrating the effect of pregnancy on the reduction of peak compound action potential amplitude of B fibers as a percent of control after 30 min exposure to different concentrations of bupivacaine. The linear regression equation for pregnant subjects was: percent block = 6.57 + 163 log (bupivacaine (M) × 10^4). The Cm = 0.185 mM. In nonpregnant subjects, the linear regression equation was: percent block = 14.0 + 110 log (bupivacaine (M) × 10^4). The Cm = 0.213 mM; Cm is the concentration of bupivacaine corresponding to 50% block.

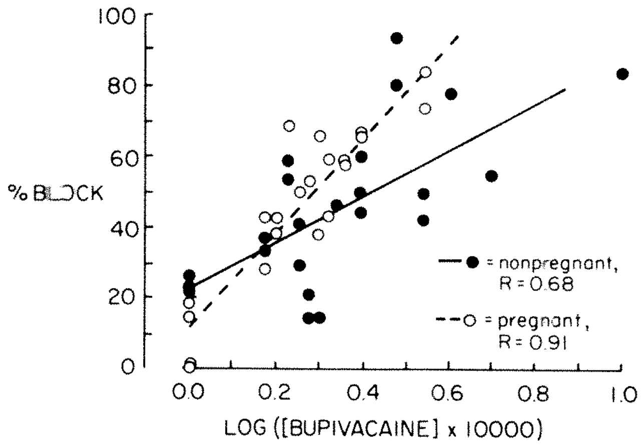

Figure 3. C Fibers. Log-linear plot illustrating the effect of pregnancy on the reduction of peak compound action potential amplitude of C fibers as a percent of control after 30 min exposure to different concentrations of bupivacaine. The linear regression equation for pregnant subjects was: percent block = 12.4 + 132^a log (bupivacaine (M) × 10^4). The Cm = 0.193 mM. In nonpregnant subjects, the linear regression equation was: percent block = 23.3 − 65.1^a log (bupivacaine (M) × 10^4). The Cm = 0.257 mM; Cm is the concentration of bupivacaine corresponding to 50% block.
$^aP < 0.01$.

by an unpaired *t*-test indicated the expected significant difference ($P < 0.05$). The number of assays was inadequate to assess the change in conduction blockade relative to the progesterone level.

Discussion

When comparing the level of epidural anesthesia obtained in pregnant and nonpregnant patients, the same dose of a local anesthetic will produce a higher level in pregnant patients (1). This result has been attributed to the space occupying and massaging effects of distended epidural veins (7) and exaggerated lumbar lordosis at term (8). However, Fagraeus et al. demonstrated increased epidural spread after lidocaine administration in women in their first trimester of pregnancy (9). They suggested that venous engorgement may not be an important determinant in the spread of epidural local anesthetics in pregnant patients because the blood volume changes are relatively small in the first trimester, and yet the increased spread of epidural anesthesia was similar in magnitude to that observed in full-term parturients. Sosis and Bodner postulated that the respiratory alkalosis of pregnancy causes a relative increase in the more diffusable free base form of the local anesthetic and results in a higher level of epidural blockade in the pregnant patient (10). However, this hypothesis has been contested by Greene (11).

In this experiment the influence of venous mechanical effects on conduction blockade was eliminated by testing isolated nerves in vitro. The data reveal a significant leftward shift in the dose–response curves for A and C fibers from the pregnant animals compared to the nonpregnant group after a 30-min exposure to bupivacaine. These results would support the conclusions of Fagraeus et al., that factors other than distension of epidural veins are responsible for the altered response of pregnant patients to epidurally administered local anesthetics.

Previous studies in isolated nerves exposed to a single concentration of bupivacaine indicated a more rapid onset of conduction blockade in nerves from pregnant animals (3). The results of the current investigation may also reflect simply an enhanced diffusion and a shorter onset of conduction block. Although equilibrium block was not completely achieved in this study, previous investigations with bupivacaine have indicated that a steady state level of conduction blockade of C fibers had occurred in approximately 30 min (12). Therefore, the differential dose–response curves for A and C fibers in nerves from pregnant and nonpregnant animals may be indicative of changes in nerves of pregnant animals that are not related solely to enhanced diffusion.

There is evidence that female sex hormones can influence the function of excitable membranes. For example, progesterone is known to decrease the rate of contraction of smooth muscle in the gallbladder (13) and the small intestine (14). Progesterone has also been shown to be effective in suppressing epileptogenic foci (15). In addition, progesterone receptors have been demonstrated in the heart and great vessels of subhuman primates (16). Mendoza and De Mello have shown that in the guinea pig, progesterone produced a small but significant increase in the cardiac resting potential, a shortening of the cardiac action potential duration, and exerted a negative inotropic action (17). Therefore, the results of the current study may indicate a basic change in the nerve membrane caused by elevated progesterone levels.

Additional studies are clearly required to determine whether the significant changes in the dose–response curves observed in this experiment are related to alterations in diffusion or represent an actual change in membrane sensitivity to local anesthetics.

References

1. Bromage PR. Epidural analgesia. Philadelphia: WB Saunders, 1978;525.
2. Bromage PR. Epidural analgesia. Philadelphia: WB Saunders, 1978:141–2.
3. Datta S, Lambert DH, Gregus J, Gissen A, Covino BC. Differential sensitivities of mammalian nerve fibers during pregnancy. Anesth Analg 1983;62:1070–2.
4. Gissen AJ, Covino BG, Gregus J. Differential sensitivities of mammalian nerve fibers to local anesthetics agents. Anesthesiology 1983;53:467–74.
5. Armitage P. Statistical methods in medical research. Boston: Blackwell Scientific Pubs. 1983:282–91.
6. Tulchinsky D, Okadh DM. Hormones in human pregnancy. IV. Plasma progesterone. Am J Obstet Gynecol 1975;121:293–9.
7. Bromage PR. Continuous lumbar epidural analgesia for obstetrics. Can Med Assoc J 1961;85:141–2.
8. Marx GF. Regional analgesia in obstetrics. Anaesthetist 1972;21:84–91.
9. Fagraeus L, Urban BJ, Bromage PR. Spread of epidural analgesia in early pregnancy. Anesthesiology 1983;58:184–7.
10. Sosis M, Bodner A. Further suggestions on epidural spread in pregnancy. Anesthesiology 1983;59:601.
11. Greene N. Dural diffusion of local anesthetics. Anesthesiology 1984;60:619.
12. Gissen AJ, Covino BG, Gregus J. The differential sensivity of mammalian nerve: III. effect of etidocaine and bupivacaine on fast/slow fibers. Anesth Analg 1982;61:570–5.
13. Ryan PJ, Pellechhi AD. Effect of progesterone pretreatment on guinea pig gall bladder. Motility in vitro. Gastroenterology 1982;83:81–3.
14. Datta S, Hey VM, Pleuvry BJ. Effects of pregnancy and associated hormones in mouse intestine in vivo and in vitro. Pflugers Arch 1984;346:85–7.
15. Backström T, Zetterlund B, Blom S, Romano M. The effects of intravenous progesterone infusions on the epileptic discharge frequency in women with partial epilepsy. Acta Neurol Scand 1984;69:240–8.
16. Lin AL, McGill HC, Shain SA. Hormone Receptors of the Baboon cardiovascular system. Circ Res 1982;50:610–16.
17. Mendoza J, DeMello WC. Influence of progesterone on membrane potential and peak tension of myocardial fibers. Cardiovasc Res 1974;8:352–61.

ANESTH ANALG
1987;66:127–31

Body Mass and Spread of Spinal Anesthesia with Bupivacaine

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PITKÄNEN MT. Body mass and spread of spinal anesthesia with bupivacaine. Anesth Analg 1987;66:127–31.

The effect of body mass on spinal anesthesia with isobaric 0.5% bupivacaine was examined in 90 patients. The first 50 patients received 3 ml isobaric 0.5% bupivacaine. Another 40 patients, selected at random to receive 3 ml of either hyperbaric or isobaric bupivacaine 0.5%, were then studied. Levels of pin-prick analgesia and motor block were tested during induction, surgery, and recovery. The effects of high spinal anesthesia on peak expiratory flow (PEF) and arterial blood gas tensions were also examined in the last 40 patients. With isobaric bupivacaine, persons with higher than normal BMI [body mass index = weight (kg) divided by height-squared (m²)], or persons who were shorter than normal had higher cephalad spread of anesthesia. With hyperbaric bupivacaine only shorter individuals developed higher levels of anesthesia. Because of considerable interindividual variability, however, these observations are of only limited clinical value in predicting the spread of bupivacaine spinal analgesia. The higher spread of analgesia was associated with a decrease in PEF, whereas, the blood gas tensions remained undisturbed.

Key Words: ANESTHETIC TECHNIQUES—spinal. COMPLICATIONS—obesity.

Certain uncontrollable or intrinsic factors may affect the distribution of solutions injected into the cerebrospinal fluid (CSF). These include age, height, anatomical configuration of the spine, and volume and density of the CSF (1–4).

Body mass index (BMI), an index of relative weight (5), has been reported to correlate with the maximum spread of analgesia when a hyperbaric solution of bupivacaine or tetracaine is used for spinal anesthesia (6). Greene, however, stated that obesity has no effect on the spread of spinal anesthesia (4). However, our retrospective analysis (1) of previous reports on patients who had had spinal anesthesia with isobaric 0.5% bupivacaine revealed a statistically significant correlation between BMI and the segmental spread of pin-prick analgesia.

To clarify the possible relationship between weight and height and the spread of spinal anesthesia, a new prospective study with isobaric or hyperbaric bupivacaine was designed. In addition, arterial blood gas tensions and peak expiratory flows were measured to evaluate the possible effect of high spinal anesthesia on respiration.

Methods

The study protocol was approved by the ethical committee of the hospital, and all patients gave informed verbal consent. Ninety orthopedic patients, ASA I–II, aged between 20 and 60 yr, about to undergo surgery on lower extremities were studied. The first 50 patients were given 3 ml of essentially isobaric plain bupivacaine 0.5% (sp. gr. 1.000 at 37°C, 1.004 at 20°C). The remaining 40 patients were selected at random to receive 3 ml of either isobaric or hyperbaric 0.5% bupivacaine (sp. gr. 1.021 at 37°C, 1.026 at 20°C). Randomization was done by blindly selecting one of 40 folded pieces of paper on which was written the solution to be used for each patient scheduled for surgery of the lower extremities. The patients were divided into groups according to their BMI [weight (kg) divided by height-squared (m^2) (kg/m^2)]. Normal BMI values for Finnish adult males are 21.1–25.9 and for females 20.2–24.6. A BMI above 30 is taken to indicate that a person is at least 20% overweight (7). The patients received diazepam 10–20 mg orally 1–2 hr before anesthesia. An intravenous infusion of Ringer's acetate solution was begun, and 200–300 ml was given before the administration of the anesthetic. The infusion was then continued at approximately 8 ml/kg during the first 20 min after the subarachnoidal injection.

The patient was placed in the horizontal lateral position and midline lumbar puncture was performed at the L3–4 intervertebral space with a 25-gauge needle

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Received from the Department of Anesthesiology, Surgical Hospital, Helsinki University Central Hospital, Helsinki, Finland. Accepted for publication July 21, 1986.

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Table 1. Patient Characteristics

	Sex F/M	Age (yr)	Height (cm)	Weight (kg)	Body Mass Index (BMI) (kg/m²)
Female BMI < 20.2 Male BMI < 21.1 (10 patients)	2/8	30.4 ± 11.3 (20–60)	178 ± 9.5 (161–190)	62.4 ± 7.7 (47–70)	19.6 ± 0.8 (17.9–20.4)
BMI > 30 (20 patients)	14/6	46.5 ± 10.2 (31–60)	165 ± 8.9 (151–184)	92.9 ± 13.7 (74–135)	33.9 ± 4.0 (30.3–47.7)
Hyperbaric group (20 patients)	9/11	40.7 ± 10.8 (21–60)	171 ± 11.8 (153–193)	85.2 ± 18.9 (51–125)	29.3 ± 5.7 (19.9–39.1)
Isobaric group (20 patients)	8/12	38.9 ± 13.1 (21–60)	172 ± 10.7 (151–187)	75.3 ± 14.7 (47–105)	25.5 ± 5.4 (17.9–35.7)

The thinnest and most obese are selected from the 70 having isobaric bupivacaine. Values are means ± SD, ranges in parentheses.

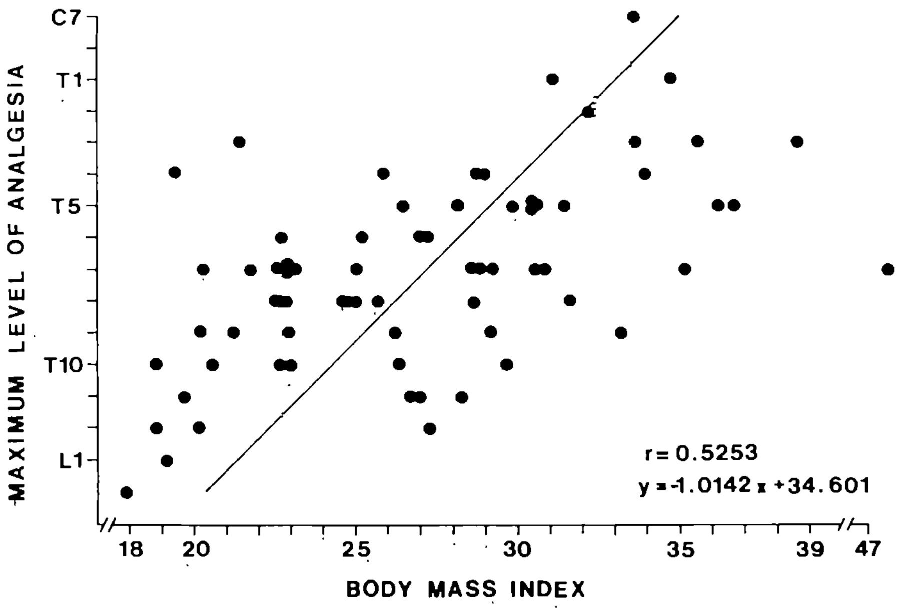

Figure 1. Relationship of body mass index (BMI) to the most cephalad level of pin-prick analgesia after injection of 3 ml isobaric 0.5% bupivacaine (70 patients).

(26-gauge in 17 patients). Cerebrospinal fluid, 0.1–0.2 ml, was aspirated to ensure correct position of the needle. Three milliliters of isobaric or hyperbaric bupivacaine 0.5% was injected within 15 sec, and thereafter a second 0.1–0.2 ml CSF was aspirated and reinjected. The patient was immediately turned to the supine horizontal position. Levels of pin-prick analgesia and motor blockade according to Bromage's scale (0–3) (8) were recorded 5, 10, 15, 20, 30, 40, 50, and 60 min after the subarachnoid injection. The testing was continued at 30-min intervals until skin sensation at the first lumbar (L1) level was normal.

The effect of spinal anesthesia on respiratory function was tested in the randomized part of the study. Before anesthesia, but after premedication, with the patient supine, a blood sample for blood–gas analysis was taken from the radial or femoral artery and peak expiratory flow (PEF) was measured. These were repeated 30 and 60 min after the subarachnoid injection. The PEF was measured three times after each blood sample was taken and the highest value was used for calculations.

ECG and blood pressure (sphygmomanometer) were monitored before and during induction, surgery, and recovery. The patients in the randomized part of the study were all interviewed on the first postoperative day, and complaints, if any, were recorded.

The statistical significance of the differences between the mean values was calculated using Student's *t*-test, between the frequencies using χ^2 test with Yates' correction for small numbers, and standard linear regression analysis was used for correlation calculations. $P < 0.05$ was considered statistically significant.

Results

Some characteristics of the patients in the study groups are presented in Table 1. With isobaric bupivacaine (70 patients), correlation coefficient (r) of 0.52 was found between BMI and the maximum level of pin-prick analgesia (Fig. 1). The correlation coefficient was less between the maximum level of pin-prick analgesia and weight ($r = 0.33$) or height ($r = -0.35$) and even less between age and the maximum level of pin-prick analgesia. When the 20 randomly selected patients who received isobaric bupivacaine were considered, there was a similar correlation coefficient ($r = 0.56$) between BMI and the maximum level of pin-prick analgesia (Fig. 2). When hyperbaric bupivacaine was used (20 patients) the highest correlation coefficient ($r = -0.48$) was found between the maximum level of pin-prick analgesia and height.

As regards the maximum level of anesthesia and PEF percentage change (the difference of PEF measured before anesthesia and the lowest value thereafter) a correlation coefficient of 0.61 was found. The mean ± SD change in PEF was 11.0% ± 13 (range 0–50) in the isobaric group and 17.0% ± 13 (range 0–43) in the hyperbaric group. Arterial blood–gas tensions remained virtually unchanged.

Table 2 compares the thinnest (BMI below normal values) and the most obese (BMI > 30) patients who had received isobaric bupivacaine. Pin-prick analgesia spread to a significantly higher segmental level in obese than it did in thin patients (Th 5 vs Th 10) ($P < 0.001$). Motor block developed more rapidly, on average, in the obese than it did in thin individuals (10 vs 26 min; $P < 0.01$). The ranges in each measured variable overlapped markedly.

Table 3 gives the results of the randomized part of the study. All patients receiving isobaric bupivacaine had total motor block in the lower extremities, whereas, 18 of the 20 patients in whom hyperbaric bupivacaine was employed had total motor block of the lower extremities. One patient in the hyperbaric group required general anesthesia for knee surgery although pin-prick analgesia had reached the level of Th 9. Two patients in hyperbaric group required intravenous fentanyl (50–100 μg). Atropine/glycopyrrolate and a vasopressor (ethylphenylephrine hydrochloride) were required in three patients who developed hypotension and bradycardia. None of the randomly selected patients in the isobaric group needed supplemental drugs for pain or for hypotension.

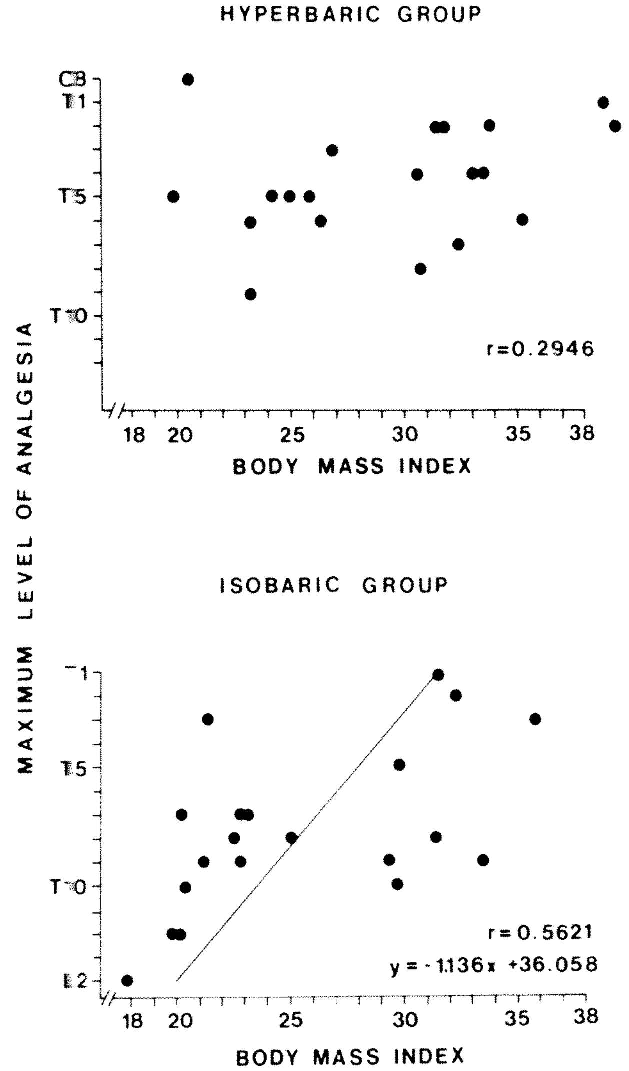

Figure 2. Relationship of body mass index (BMI) to the most cephalad level of pin-prick analgesia in the randomized part of the study after injection of 3 ml of either hyperbaric or isobaric 0.5% bupivacaine (20 + 20 patients).

The differences between the groups in the number of total motor blocks of the lower extremities or need for additional medication were not statistically significant. Mean changes of arterial systolic pressure when compared with preanesthetic value were not significantly different (18% ± 12 SD, range 0–50 in the hyperbaric group and 12% ± 10 SD, range 0–44 in the isobaric group. Three patients in the first isobaric group (50 patients) required fentanyl; ethylphenylephrine hydrochloride was needed for hypotension in one patient, and two patients developed a heart rate deemed low enough to require atropine.

There were no complaints of postdural puncture headache. Postoperatively, one patient in the isobaric group complained of backache and another had nau-

Table 2. Characteristics of Results in the Thinnest and Most Obese Patients When Isobaric Bupivacaine Was Used

	Maximum spread of pin-prick analgesia (segments)	Time to analgesia reaching the L-1 segment (min)	Time to maximum spread of pin-prick analgesia (min)	Time to total motor block (min)	Time to recovery of two highest segments (min)	Time to recovery of L-1 segment (min)
Female BMI < 20.2 Male BMI < 21.1	T-10 (12.8 ± 3.0) (L2–T4)	15.0 ± 8.3 (5–30)	33.0 ± 12.5 (10–50)	26 ± 10.7 (5–40)	147 ± 36 (90–210)	163 ± 45 (90–240)
BMI > 30	T-5 (18.4 ± 2.6) (T9–C7)	6.3 ± 2.8 (5–15)	24.0 ± 13.7 (10–60)	10 ± 6.0 (5–30)	105 ± 37 (40–180)	180 ± 26 (120–210)
p	<0.001	<0.001	ns	<0.01	<0.01	ns

Values are means ± SD, ranges in parentheses.

Table 3. Characteristics of Results From the Randomized Part of the Study

	Maximum spread of pin-prick analgesia (segments)	Time to analgesia reaching the L-1 segment (min)	Time to maximum spread of pin-prick analgesia (min)	Time to maximum motor block (min)	Time to recovery of two highest segments (min)	Time to recovery of L-1 segment (min)
Hyperbaric group (20 patients)	T-4 (18.7 ± 2.4) (T9–C8)	5.3 ± 1.1 (5–10)	26 ± 12.8 (10–60)	11.5 ± 10.0 (5–20)	96 ± 24 (60–150)	167 ± 30 (120–210)
Isobaric group (20 patients)	T-8 (15.3 ± 3.4) (L2–T1)	9.7 ± 6.1 (5–20)	29 ± 13.7 (10–50)	18.3 ± 10.5 (5–40)	115 ± 32 (40–180)	181 ± 36 (120–240)
p	<0.001	<0.01	ns	<0.05	ns	ns

Values are means ± SD, ranges in parentheses.

sea. In the hyperbaric group one patient had urinary incontinency, a second complained of backache, and a third had episodes of vomiting during the first postoperative night.

Discussion

A relatively low *r* value (around 0.5) indicates that height, weight, or BMI have only little clinical significance in predicting the spread of spinal anesthesia with plain bupivacaine. This study substantiated reports that the predictability of the spread of analgesia especially with isobaric bupivacaine is poor (1,9). The ranges of the maximum spread were great and overlapped considerably. However, the most obese patients showed a tendency towards higher cephalad spread, more rapid onset, and more rapid recovery from anesthesia when compared with the thinnest patients.

In contrast to the results of a previous study on isobaric bupivacaine (1), age did not correlate with the maximum spread of pin-prick analgesia. This discrepancy is apparent rather than real, because in order to eliminate another possible factor that might affect results in the present study neither young (under 20) nor elderly (above 60 yr) patients were included in the study. The present findings from a homogenous age-range seem to strengthen the generally accepted clinical view that age plays only a minor role as a reliable predictor of the segmental spread of spinal analgesia.

In the small prospective group of patients given 15 mg hyperbaric bupivacaine, the correlation between BMI and the maximum spread of sensory analgesia was poorer than when isobaric bupivacaine was used. Moore (6) has shown in 435 patients, in four different groups, that higher BMI was associated with a higher spread of pin-prick analgesia when hyperbaric bupivacaine or tetracaine (7.5 or 12 mg) were used. As seen in the present study, however, when larger amounts of bupivacaine (15 mg) are used the spread of hyperbaric solutions in the CSF may be primarily governed by baricity (4). The position of the patient at the time of the injection of the local anesthetic and for some time thereafter is crucial when the baricity of the solution differs from that of the CSF.

There was a clear reduction in peak-flow in patients with higher cephalad spread of analgesia. This result is in accordance with the report of Freund et al. (10), who noted that a greater spread of motor and sensory block into the thoracic area during spinal and epidural anesthesia causes a proportionally larger decrease in the expiratory reserve volume. In the present study, with patients breathing room air neither respiratory depression nor arterial hypoxemia were detected despite clear reductions in PEF. Apparently, even in obese patients lying in a horizontal position, diaphragmatic resting ventilation is sufficient. Difficulties may arise, however, when Trendelenburg's position might be required, for instance in hypotension in an obese patient with an associated high level of spinal anesthesia.

In the randomized part of the study comparing hyperbaric and isobaric bupivacaine, more rapid onset of motor and sensory block at the L-1 segment was observed when the hyperbaric solution was used. Due to great interindividual variations in both groups, these differences probably have little clinical importance. On average, the cephalad spread of sensory analgesia was four segments higher in the hyperbaric bupivacaine group than in the isobaric bupivacaine group, supporting the reports by Chambers et al. and Brown et al. (11,12). The clinical significance of this finding is also limited due to great interindividual variations in both groups. There was no difference in the mean decrease of systolic arterial pressure between the patient groups. In this age range, hypotension during bupivacaine spinal anesthesia does not impose a major clinical problem (1,13).

In conclusion, the effect of height, weight, or body mass as measured by BMI (kg/m^2) on the spread of spinal anesthesia with bupivacaine was found to be small. There was some tendency to increase in the level of pin-prick analgesia with increase in BMI, but because of considerable interindividual overlapping the clinical significance of this finding is limited.

The author acknowledges with thanks the numerous discussions and support by Per H. Rosenberg, MD, and Marjatta Tuominen, MD, during the course of the study and the preparation of the manuscript.

References

1. Pitkänen M, Haapaniemi L, Tuominen M, Rosenberg PH. Influence of age on spinal anaesthesia with isobaric 0.5% bupivacaine. Br J Anaesth 1984;56:279–84.
2. Cameron AE, Arnold RW, Ghoris MW, Jamieson V. Spinal analgesia using bupivacaine 0.5% plain. Anaesthesia 1981; 36:318–22.
3. Lund PC. Principles and practice of spinal anesthesia. Charles C Thomas: Springfield, 1971:112–5.
4. Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. Anesth Analg 1985;64:715–30.
5. Keys A, Fidanza F, Karvonen MJ, Kimura N, Taylor HL. Indices of relative weight and obesity. J Chron Dis 1972;25:329–43.
6. Moore DC. Factors influencing spinal anesthesia. Regional Anesthesia 1982;7:20–5.
7. Heliövaara M, Aromaa A. Height, weight and obesity of Finnish adults. Publications of the Social Insurance Institution, Finland, ML:19, Helsinki 1980:91–2.
8. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine (suppl.). Acta Anaesthesiol Scand 1965;16:55–69.
9. Logan MR, McClure JH, Wildsmith JAW. Plain bupivacaine: an unpredictable spinal anaesthetic agent. Br J Anaesth 1986;58:292–6.
10. Freund FG, Bonica JJ, Ward RJ, Akamatsu TJ, Kennedy Jr WF. Ventilatory reserve and level of motor block during high spinal and epidural anesthesia. Anesthesiology 1967;28:834–7.
11. Chambers WA, Edström HH, Scott DB. Effect of baricity on spinal anaesthesia with bupivacaine. Br J Anaesth 1981;53:279–82.
12. Brown DT, Wildsmith JAW, Covino BG, Scott DB. Effect of baricity on spinal anaesthesia with amethocaine. Br J Anaesth 1980;52:589–95.
13. Pitkänen M, Tuominen M, Rosenberg PH. Bupivacaine spinal anesthesia compared with etidocaine epidural anesthesia for orthopedic surgery in old and young patients. Regional Anesthesia 1985;10:62–7.

ANESTH ANALG
1987;66:132–6

A Clinical Study of Sensitivity to Sodium Nitroprusside during Controlled Hypotensive Anesthesia in Young and Elderly Patients

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WOOD M, HYMAN S, WOOD AJJ. A clinical study of sensitivity to sodium nitroprusside during controlled hypotensive anesthesia in young and elderly patients. Anesth Analg 1987;66:132–6.

Aging has important effects on the cardiovascular system; baroreceptor reflex function decreases and the elderly are more resistant to both β-receptor agonists and antagonists. The purpose of the present clinical study was to determine the relationship between age and sensitivity to sodium nitroprusside in 16 patients during deliberate hypotensive anesthesia by determining the blood pressure changes in young and elderly patients to incremental increases in dose of sodium nitroprusside. A dose–response curve relating change in mean blood pressure to dose of sodium nitroprusside ($\mu g \cdot kg^{-1} \cdot min^{-1}$) was constructed for each patient; the slope of this line is a measure of "sensitivity." The change in mean arterial blood pressure per $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside dose (i.e., slope), showed a significant correlation with age ($r = 0.766$, $P < 0.001$), demonstrating that sensitivity to sodium nitroprusside increases with advancing years. The maximum change in heart rate produced by nitroprusside showed a reciprocal correlation with age ($r = -0.791$, $P < 0.001$). There was no significant correlation between age and maximum change in plasma norepinephrine or epinephrine concentrations during nitroprusside infusion. The increased sensitivity to nitroprusside might have been due to 1) diminished baroreflex activity, 2) resistance of cardiac adrenergic receptors to catecholamine stimulation, or 3) alteration in sensitivity to the direct vasodilating effects of sodium nitroprusside. Whatever the mechanism, however, this clinical study has shown that lower doses of nitroprusside should be used in elderly patients to achieve the same degree of hypotension achieved in younger patients.

Key Words: ANESTHETIC TECHNIQUES, HYPOTENSIVE—nitroprusside. PHARMACOLOGY—nitroprusside. AGE FACTORS—nitroprusside response.

Although surgery for the elderly is now routine and in spite of the increasing demographic importance of this age group, relatively little attention has been focused on their responses to drugs. It is well recognized that elderly patients experience an increased incidence of adverse drug reactions (1). Factors that may be responsible for changes in drug response in the elderly include first, altered drug disposition, and second, changes in receptor-response relationships, i.e., "sensitivity."

Aging has important effects on the cardiovascular system; baroreceptor reflex function decreases with advancing age, producing less cardiac slowing in response to phenylephrine-induced increase in blood pressure (2). Furthermore, there is an age-related decrease in the sympathetic response to exercise (3) and the increase in left ventricular ejection fraction that occurs with exercise is less in elderly subjects (4). Hence, the cardiovascular pathophysiologic changes that occur in the elderly may result in the elderly being less able to compensate for a given decrease in blood pressure. The response to hypotension is reflexly mediated through an increase in sympathetic nervous system activity via the baroreceptor system, so that plasma norepinephrine levels increase in response to sodium nitroprusside-induced hypotension (5). Plasma norepinephrine concentrations also increase with age (6), while the elderly become more resistant to both the β-receptor agonist isoproterenol and antagonist propranolol (7). Increased sensitivity to nitroprusside in the elderly may be due to either alteration in sensitivity to the direct vasodilating effects, or to a decrease in the compensatory reflexes produced by a decrease in blood pressure. Changes in the activity of the homeostatic reflexes might be due first, to diminished baroreceptor responses accompanied by a less pronounced increase in catecholamine concentration or second, to a decrease in response to in-

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Supported by US PHS Grants AG 01395 and HL 14192 and the Study Center for Anesthesia Toxicology. Presented in part at the annual meeting of the ASA in 1983.

Received from the Departments of Anesthesiology and Pharmacology, Vanderbilt University Medical School, Nashville, Tennessee. Accepted for publication July 28, 1986.

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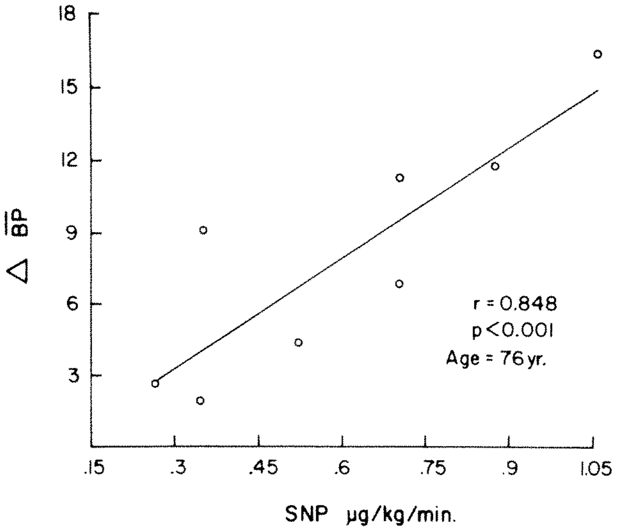

Figure 1. Change in mean arterial blood pressure per μg·kg⁻¹·min⁻¹ sodium nitroprusside dose in a 76-yr-old patient.

creased plasma catecholamine levels produced by stimulation of the baroreceptor reflex.

The purpose of the present study, therefore, was to determine the relationship between age and sensitivity to sodium nitroprusside during controlled hypotensive anesthesia by determining blood pressure changes to incremental increasing doses of sodium nitroprusside in young and elderly patients.

Methods

The study was approved by the Institutional Review Board, and all patients gave written informed consent prior to participation in the study. Sixteen patients (nine females and seven males, aged 18–76 yr, ASA physical status II or III) undergoing neurosurgical resection of cerebral aneurysms were studied. Patients receiving β-adrenergic receptor blocking agents or calcium antagonists were excluded from the study. No patients were currently receiving antihypertensive medication; one patient had methyldopa discontinued 4 days preoperatively. The patients were anesthetized with a thiopental (4 mg/kg) nitrous oxide–oxygen, muscle relaxant, narcotic technique; six patients received fentanyl 0.05 mg at approximately 40-min intervals, and ten patients received a sufentanil infusion of 0.3 μg·kg⁻¹·min⁻¹. In seven patients, isoflurane (0.25–0.5% end-tidal as measured by mass spectrometry) was added to control moderate increase in blood pressure, such as occurs during removal of the bone flap; if isoflurane was required it was then continued at these end-tidal concentrations throughout the operative procedure. The patients were moderately hyperventilated to achieve Pa_{CO_2} values of between 28 and 32 mm Hg.

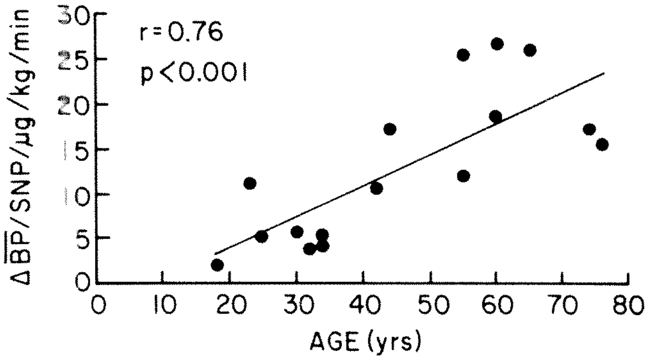

Figure 2. Age and sensitivity to sodium nitroprusside. Change in mean arterial blood pressure per μg·kg⁻¹·min⁻¹ nitroprusside dose (i.e., slope) for each patient plotted against age (yr). The equation of the line is: change in mean BP/nitroprusside dose μg·kg⁻¹·min⁻¹ = −3.038 + 0.35 × age.

Arterial pressure was monitored using an indwelling arterial cannula. Sodium nitroprusside (100 μg/ml) was infused with graded increases in dose starting at 0.2 μg·kg⁻¹·min⁻¹ to produce an average mean arterial blood pressure of 62.7 mm Hg (SEM ± 2.3). At each dose of sodium nitroprusside, mean blood pressure and heart rate were recorded. For each dose of nitroprusside, change in mean blood pressure from control values obtained during a control period approximately 5 min before commencement of the nitroprusside infusion when stable levels of anesthesia had been attained was calculated. A dose–response curve relating change in mean blood pressure to dose of sodium nitroprusside (μg·kg⁻¹·min⁻¹) was constructed for each patient using linear regression analysis, and the slope calculated from the equation of the line. The slope of this line (change in mean arterial blood pressure per μg·kg⁻¹·min⁻¹ sodium nitroprusside dose), is thus, a measure of blood pressure sensitivity; increased slope implies that a greater blood pressure reduction is produced by a given dose of sodium nitroprusside.

Samples of arterial blood for the measurement of plasma epinephrine and norepinephrine concentrations were taken both immediately prior to the commencement of sodium nitroprusside infusion and, during the period of sodium nitroprusside infusion, at approximately 5-min intervals, until a stable infusion rate of nitroprusside was obtained to produce the desired level of hypotension and then at approximately 30-min intervals thereafter. At the same time each blood sample was being drawn for measurement of plasma norepinephrine and epinephrine concentrations, the patients' heart rates and mean blood pressures were recorded. Blood samples for mea-

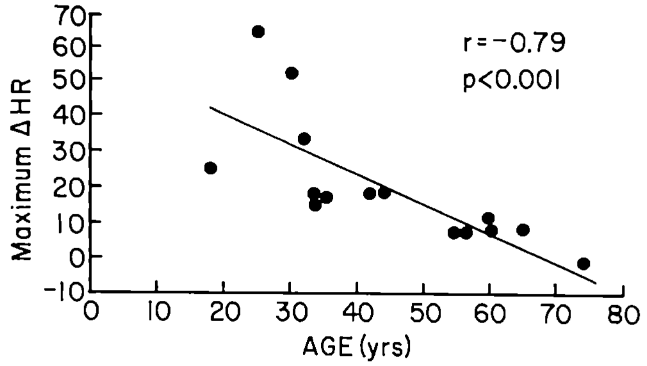

Figure 3. Maximum change in heart rate during sodium nitroprusside-induced hypotension plotted against age ($n = 15$; one patient was excluded from analysis because the heart rate was 110 beats/min prior to sodium nitroprusside infusion).

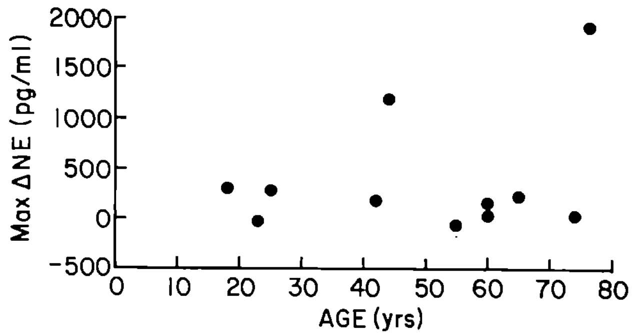

Figure 4. Lack of correlation between maximum change in plasma norepinephrine concentration during sodium nitroprusside infusion (when compared with control value immediately prior to commencement of infusion) plotted against age ($n = 11$, $r = 0.267$, $P = 0.4$).

surement of catecholamines were taken into tubes (on ice) containing reduced glutathione, and then assayed for norepinephrine and epinephrine with a modification of the technique of Passon and Peuler (8), in which methylated derivatives of catecholamines are produced in the presence of catechol-O-methyltransferase and tritiated S-adenosylmethionine and then separated by thin layer chromatography. Statistical analysis was by linear regression analysis, with $P < 0.05$ as the minimal level of statistical significance.

Results

Figure 1 shows the dose–response curve relating change in blood pressure to sodium nitroprusside dose ($\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$) for a 76-yr-old patient, demonstrating a progressive decrease in mean blood pressure with increasing dose of sodium nitroprusside ($r = 0.848$; $P < 0.001$). The coefficient of correlation for the slope (change in blood pressure/dose of nitroprusside) of the line for each individual patient varied from $r = 0.506$ to $r = 0.995$. For five patients, there were insufficient data to appropriately use linear regression analysis, and then maximum change in blood pressure divided by dose of sodium nitroprusside in $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ was used to determine blood pressure sensitivity to nitroprusside.

The change in mean arterial blood pressure per $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ sodium nitroprusside dose for each individual patient (i.e., slope, calculated as described above) was then plotted against age. There was a significant correlation with age ($r = 0.766$, $P < 0.001$) (Fig. 2), demonstrating that blood pressure sensitivity to sodium nitroprusside increases with advancing years and that any given dose of sodium nitroprusside produces a greater fall in blood pressure in the elderly than in the young.

The maximum increase in heart rate produced by nitroprusside showed a significant reciprocal correlation ($r = -0.791$, $P < 0.001$) (Fig. 3) with age, indicating that elderly patients do not have as great an increase in heart rate as do younger subjects during nitroprusside-induced hypotension.

There was no significant correlation between age and maximum change in plasma norepinephrine (Fig. 4) or epinephrine concentrations during sodium nitroprusside infusion. In addition, age was not significantly correlated with changes in heart rate/norepinephrine concentration.

Discussion

It has been reported previously that although age does not significantly correlate with the dose of nitroprusside required to produce a mean blood pressure of 65 mm Hg, there is a significant correlation between the age/weight ratio and nitroprusside infusion (μg/min) (9). However, drug sensitivity is best defined by the construction of individual dose–response curves. Our study, utilizing individual dose–response curves relating blood pressure changes to graded increases in nitroprusside dose shows that the elderly are more sensitive to sodium nitroprusside during controlled hypotensive anesthesia, and that lower doses should be used in this age group.

The effects of anesthetic technique on baroreceptor function and nitroprusside sensitivity must be considered in this clinical study. Halothane and enflurane reduce nitroprusside dose requirements in dogs (10,11). In addition, inhalational anesthetics depress baroreceptor function, although the depression of arterial baroreflex heart rate responses under isoflurane anesthesia appears to be less pronounced than those during enflurane or halothane (12–14). Morphine, diazepam, nitrous oxide/oxygen anesthesia depresses baroreflex heart rate in humans to a degree similar to that seen with the potent volatile anesthetics (15). Although sufentanil, fentanyl and isoflurane were given to our patients, there were no differences in anesthetic technique with age, and, therefore, in the clinical setting of narcotic-relaxant anesthesia with addition of light isoflurane anesthesia, the dose of nitroprusside should be reduced in elderly patients undergoing profound hypotensive anesthesia.

The hypotensive effects of sodium nitroprusside are the resultant of both the primary direct vasodilator effects of nitroprusside on vascular smooth muscle, which tend to lower blood pressure, and compensatory homeostatic reflexes that act to limit the decrease in blood pressure. It is doubtful whether the increased sensitivity to nitroprusside in the elderly is due to altered sensitivity to the direct vasodilator effects of sodium nitroprusside, because extensive animal model investigation has failed to show any altered vasodilator responses to direct acting vasodilators in elderly animals (16,17). Further work should be undertaken to define the direct vasodilatory effects of nitroprusside in young and elderly patients, both in the clinical research laboratory setting and during controlled hypotensive anesthesia, when much greater decreases in blood pressure are produced.

Baroreflex function, important in blood pressure homeostasis during hypotension and postural changes, has been shown to decline with both hypertension (18) and age (2). Nitroprusside administration results in increased circulating catecholamine concentrations (19,20) that reflect increased sympathetic nervous system activity and may account for the tachycardia often seen during sodium nitroprusside-induced hypotension. Elderly hypertensive patients demonstrate increased sensitivity to nitroprusside when mean arterial blood pressure is reduced by approximately 20% in the clinical research laboratory (21,22), accompanied by a reduced heart rate response (21). The present study has shown that, during anesthesia, when nitroprusside is administered clinically to produce the greater decreases in blood pressure required for profound hypotension, the elderly are more sensitive to nitroprusside. We were also able to demonstrate that there are smaller increases in heart rate in elderly patients during hypotension, despite similar changes in catecholamine concentrations in both young and elderly patients, implying resistance to the β-receptor mediated tachycardia produced by catecholamines.

The explanation for these changes may in part lie in the altered β-receptor function seen in the elderly. Recent work has shown that although there is no change in β-receptor density in the elderly (23,24), the affinity of the β-receptor for adrenergic agonists decreases with advancing years (24). In addition, when subjects assume the erect posture after lying supine, β-receptor affinity decreases in young subjects, whereas, β-receptor affinity (already reduced) remains the same in elderly patients (24). Although resting plasma norepinephrine concentrations are higher in elderly subjects, when young and elderly subjects stand up they have similar increases in plasma catecholamine concentrations. Physiological changes in circulating catecholamines "down regulate" β-receptor function in young individuals (25), but impairment in the coupling of the β-adrenergic receptor adenylate cyclase complex in the elderly probably accounts for the reduction in β-adrenergic responsiveness seen in this group of subjects (7).

In summary the increased sensitivity to nitroprusside in elderly patients shown in this clinical study might have been due to 1) diminished baroreceptor reflex activity, 2) resistance of cardiac adrenergic receptors to catecholamine stimulation, or 3) altered sensitivity to the direct vasodilatory effects of sodium nitroprusside. However, the fact that we found similar increases in plasma epinephrine and norepinephrine concentrations in both young and elderly patients during hypotensive anesthesia, despite the diminished heart rate responses in elderly patients, suggests that the explanation for the increased sensitivity to nitroprusside in the elderly may in part be a manifestation of resistance of cardiac adrenergic receptors to catecholamine stimulation as a consequence of reduced β-adrenergic receptor affinity. The relationship between the various physiologic factors that interplay to cause a decrease in blood pressure in response to the administration of the vasodilator, nitroprusside, is complex and further work is required to define the altered cardiovascular responses that occur during anesthesia and surgery in the elderly.

References

1. Miller RR. Drug surveillance utilizing epidemiologic methods: A report from the Boston Collaborative Drug Surveillance Program. Am J Hosp Pharm 1973;30:584–92.
2. Duke PC, Wade JG, Hickey RF, Larson CP. The effects of age on baroreceptor reflex function in man. Can Anaesth Soc J 1976;23:111–24.
3. Conway J, Wheeler R and Sannerstedt R. Sympathetic nervous activity during exercise in relation to age. Cardiovasc Res 1971;5:577–81.
4. Port S, Cobb FR, Coleman RE, Jones RH. Effect of age on the response of the left ventricular ejection fraction to exercise. N Engl J Med 1980;303:1133–7.
5. Knight PR, Lane GA, Hensinger RN, Bolles RS, Bjoraken DG. Catecholamine and renin-angiotensin response during hypotensive anesthesia induced by sodium nitroprusside or trimetaphan camsylate. Anesthesiology 1983;59:248–53.

6. Ziegler MG, Lake CR, Kopin IJ. Plasma noradrenaline increases with age. Nature 1976;261:333–5.
7. Vestal RE, Wood AJJ, Shand DG. Reduced beta-adrenoreceptor sensitivity in the elderly. Clin Pharmacol Ther 1979;26:181–6.
8. Passon PG, Peuler JD. A simplified radiometric assay for plasma norepinephrine and epinephrine. Analytical Biochemistry 1973;51:618–31.
9. Lawson NW, Thompson DS, Nelson CL, Flacke JW, Seifen AB. A dosage nomogram for sodium nitroprusside-induced hypotension under anesthesia. Anesth Analg 1976;55:574–81
10. Bedford RF. Increasing halothane concentrations reduce nitroprusside dose requirement. Anesth Analg 1978;57:457–62.
11. Bedford RF. Sodium nitroprusside: hemodynamic dose–response during enflurane and morphine anesthesia. Anesth Analg 1979;58:174–8.
12. Duke PC, Fownes D, Wage JG. Halothane depresses baroreflex control of heart rate in man. Anesthesiology 1977;46:184–7.
13. Morton M, Duke PC, Ong B. Baroreflex control of heart rate in man awake and during enflurane and enflurane–nitrous oxide anesthesia. Anesthesiology 1980;52:221-3.
14. Kortly KJ, Ebert T, Vucins E, Igler FO, Barney JA, Kampine JP. Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. Anesthesiology 1984;60:173–9.
15. Kortly KJ, Ebert JJ, Vucins EJ, Roerig DL, Kampine JP. Baroreceptor reflex control of heart rate during morphine sulfate, diazepam, N_2O/O_2 anesthesia in humans. Anesthesiology 1984;61:558–63.
16. Fleish JH, Maling HM, Brodie BB. Beta-receptor activity in aorta: Variations with age and species. Circ Res 1970;26:151–62.
17. Fleisch JH, Hooker CS. The relationship between age and relaxation of vascular smooth muscle in the rabbit and rat. Circ Res 1976;38:243–9.
18. Vlachakis ND, Mendlowitz M, DeGusman D. Diminished baroreceptor sensitivity in elderly hypertensives. Atherosclerosis 1976;24:243–9.
19. Grossman SH, Davis D, Gunnells JC, Shand DG. Plasma norepinephrine in the evaluation of baroreceptor function in humans. Hypertension 1982;4:566–71.
20. Lin M-S, McNay JL, Shepherd AMM, Keeton TK. Effects of hydralazine and sodium nitroprusside on plasma catecholamines and heart rate. Clin Pharmacol Ther 1983;34:474–80.
21. McGarry K, Laher M, Fitzgerald D, Horgan J, O'Brien E, O'Malley K. Baroreflex function in elderly hypertensives. Hypertension 1983;5:763–6.
22. Irvine NA, Shepherd AMM. Age and blood pressure determine vasodepressor response to sodium nitroprusside. J Cardiovasc Pharmacol 1984;6:816–21.
23. Abrass IB, Scarpace PJ. Human lymphocyte beta-adrenergic receptors are unaltered with age. J Gerontol 1981;36:298–301.
24. Feldman RD, Limbird LE, Nadeau J, Robertson D, Wood AJJ. Alteration in leukocyte beta-receptor affinity with aging—A potential explanation for altered beta-adrenergic sensitivity in the elderly. N Engl J Med 1984;310:815–9.
25. Fraser J, Nadeau J, Robertson D, Wood AJJ. Regulation of human leukocyte beta receptors by endogenous catecholamines. J Clin Invest 1981;67:1777–84.

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Hemodynamic Effects of Esmolol in Chronically β-Blocked Patients Undergoing Aortocoronary Bypass Surgery

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Hemodynamic effects of esmolol in chronically β-blocked patients undergoing aortocoronary bypass surgery.
Anesth Analg 1987;66:137–41.

The hemodynamic effects of esmolol were studied in 40 patients scheduled for elective coronary artery surgery to determine whether the administration of esmolol in chronically β-blocked patients would result in additional attenuation of sympathetically mediated hemodynamic stress responses to noxious stimuli. Patients were randomly assigned to receive IV infusions of esmolol or 5% dextrose in water (D_5W). All received their regular dose of β-adrenergic blocker within 6 hr of surgery and were anesthetized with diazepam, pancuronium, and enflurane. Increases (>25% above baseline) in systolic blood pressure were treated with sodium nitroprusside (SNP). Esmolol was started before induction of anesthesia and continued until 5 min after maximal sternal spread. There were no statistically significant differences between the esmolol and control groups in any hemodynamic parameter during induction, intubation, skin incision, and sternotomy. Only at 5 min after maximal sternal spread was there a statistically significant lower systolic blood pressure in the esmolol-treated group. However the incidence and magnitude of SNP use in the control group was significantly ($P < 0.05$) greater. Thus, the lower blood pressure, in the absence of changes in systemic vascular resistance, cardiac index, heart rate, and pulmonary capillary wedge pressure points toward a decrease in myocardial contractility, suggesting that the addition of esmolol to chronically used β-blockers resulted in an additional negative inotropic effect. We conclude that in patients with coronary artery disease in whom chronic β-blocker therapy is continued until the time of surgery, esmolol does not further attenuate the heart rate response but does attenuate the increase in blood pressure. The presumed reason for this finding is that esmolol in the dose employed does not occupy sufficient additional β-receptors to produce added β-adrenergic blockade and therefore does not further attenuate heart rate response to sympathetic nervous system stimulation. Blood pressure is probably decreased because of esmolol's negative inotropic effect.

Key Words: SYMPATHETIC NERVOUS SYSTEM—β-adrenergic antagonists, esmolol. HEART—myocardial function, β-adrenergic blockade.

Esmolol (methyl 3-(4-(2-hydroxy-3-(isopropylamino)-propoxy)phenyl) proprionate hydrochloride) is a short-acting β-adrenergic blocker (1). It has been used to attenuate the heart rate (HR) and blood pressure (BP) response in anesthetized patients with normal ventricular function (2). Sympathetic nervous system mediated increases in HR and BP are known to occur with the stimuli of laryngoscopy and intubation, skin incision, median sternotomy, and other types of surgical stimulation (3–6). These hemodynamic changes are undesirable, especially in patients with coronary artery disease, because they increase myocardial oxygen consumption and may cause myocardial ischemia. Menkhaus et al. studied the use of esmolol in patients undergoing coronary artery bypass grafting (CABG) in whom "chronic" β-blockers had been withheld for up to 16 hr, and found that esmolol attenuated the hemodynamic response to endotracheal intubation (2). We studied a similar group of CABG patients in whom β-blocker therapy was continued until surgery to assess whether esmolol attenuates the hyperdynamic response in patients already clinically β-blocked.

Methods

Forty patients were enrolled in the study after Institutional Review Board approval and written informed consent were obtained. All were scheduled for elective coronary artery bypass graft surgery. Exclusion criteria included recent myocardial infarction (within 1 week of surgery), cardiogenic shock, asthma, and atrial flutter or fibrillation, as well as atrioventricular

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This study was funded by American Critical Care.

Received from the Division of Cardiothoracic Anesthesia, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina. Accepted for publication August 18, 1986.

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Table 1. Esmolol Infusion Regimen

Infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Duration (min)
500	1
100	4
500	1
200	4
500	1.5
300	Until 5 min after sternal spread

Table 2. Demographic Characteristics

	Control (n = 21)	Esmolol (n = 19)
Age (yr)[a]	59.2 (43–73)	57 (40–69)
Weight (kg)[a]	79.3 (58–106)	77.6 (53–100)
BSA (m^2)[a]	1.88 (1.69–2.22)	1.89 (1.53–2.21)
LVEDP (mm Hg)[b]	17.5 ± 4.1	17.0 ± 6.7
EF (%)[b]	58.5 ± 11.7	57.8 ± 9.5
CI ($L \cdot min^{-1} \cdot m^{-2}$)[b]	2.6 ± 0.9	2.9 ± 1.0

Abbreviations: BSA, body surface area; LVEDP, left ventricular end-diastolic pressure; EF, ejection fraction; CI, cardiac index.

[a] Values are mean, with range in parentheses.

[b] Mean ± SD.

Table 3. Antianginal Therapy

	Control (n = 20)	Esmolol (n = 19)
β-Blockers		
atenolol	7	8
metoprolol	3	1
nadolol	0	1
propranolol	10	9
Calcium channel blockers	14	11
Nitrates	11	11

conduction blocks greater than first degree. Patients were randomized to receive an esmolol infusion (n = 19) or 5% dextrose in water (D_5W) infusion (n = 21). The study was not blinded. All patients were premedicated with 0.15 mg/kg of diazepam orally, 0.1 mg/kg of morphine intramuscularly, and scopolamine, 0.2 mg intramuscularly. Patients received their last dose of β-blocker within 6 hr of surgery, and usually 3 hr before surgery. Electrocardiogram leads II and V_5 as well as radial and pulmonary arterial pressures were monitored continuously in all patients. As an additional safeguard all patients received a pulmonary artery catheter with pacing capabilities. Thermodilution cardiac output was measured in duplicate at periodic intervals. After a 10-min stabilization period 19 patients received an infusion of esmolol according to the infusion scheme outlined in Table 1, and 21 received a slow infusion of D_5W.

Seven minutes after initiating the esmolol infusion, anesthetic induction was begun in all patients. Anesthesia induction was performed with diazepam, 0.5 mg/kg IV pancuronium 100 μg/kg IV and 0.4% inspired enflurane. Tracheal intubation occurred 4 min after induction of anesthesia. Nitrotriglycerin (NTG) was administered if there were signs of myocardial ischemia (ST-depression or ST-elevation greater than 1 mm and/or an increase of pulmonary artery diastolic pressure (PAD) greater than 30% over control). Increases in systolic arterial pressure (SAP) greater than or equal to 25% of control and sustained over 5 min or SAP levels 20 mm Hg. above the highest control SAP and sustained over 5 min were treated with sodium nitroprusside (SNP).

Hemodynamic data were collected immediately before the start of the esmolol infusion (baseline), 1 and 3 min after induction of anesthesia, 1 and 5 min after endotracheal intubation, 5 min after skin incision, 5 min after sternotomy, and at the end of the esmolol infusion period (5 min after maximal sternal spread). During the esmolol infusion, venous blood obtained from the internal jugular vein on the contralateral side from the esmolol infusion was sampled for measurement of plasma esmolol levels at the time of induction of anesthesia, intubation, skin incision, sternotomy, and maximal sternal spread. Blood esmolol levels were determined by a gas chromatographic–mass spectrometric method in the analytical laboratory of American Critical Care (McGaw Park, Illinois). A CK-MB level was determined 10 hr after discontinuation of cardiopulmonary bypass.

All hemodynamic and blood concentration data are expressed as means ± SD. Between-group comparisons were performed by a one-factor analysis of variance computed at each interval. When the analysis of variance F-test statistic was significant, pair-wise comparison was performed by Fisher's protected least significant difference test. Comparisons of nonparametric data were performed using the χ^2 statistic for contingency tables. Differences were considered to be statistically significant if $P < 0.05$. All statistical computations were performed with the aid of the Statistical Analysis System.

Results

Patients in the control and treatment groups had similar demographic characteristics (Table 2) and were on similar chronic antianginal therapy (Table 3). The control group included one NYHA Class II, two NYHA Class III, and eighteen NYHA Class IV patients. Esmolol-treated patients included three NYHA Class II, three NYHA Class III, and thirteen Class IV.

Table 4. Hemodynamic Parameters

	Baseline	Induction + 1	Induction + 3	Intubation + 1	Intubation + 5	Skin incision + 5	Sternotomy + 5	Maximum sternal spread + 5
HR (beats/min)								
Control	55 ± 7	74 ± 10	64 ± 8	79 ± 12	80 ± 13	76 ± 13	72 ± 14	70 ± 12
Esmolol	53 ± 5	72 ± 9	68 ± 7	77 ± 12	77 ± 13	69 ± 15	66 ± 16	64 ± 12
SAP (mm Hg)								
Control	142 ± 15	126 ± 16	133 ± 14	169 ± 23	167 ± 23	171 ± 31	148 ± 26	139 ± 23[a]
Esmolol	138 ± 20	115 ± 18	119 ± 21	156 ± 26	148 ± 22	139 ± 29	129 ± 32	121 ± 22[a]
MAP (mm Hg)								
Control	88 ± 8	80 ± 7	84 ± 7	109 ± 11	106 ± 13	113 ± 19	98 ± 15	93 ± 16
Esmolol	87 ± 11	77 ± 12	78 ± 13	106 ± 17	99 ± 13	97 ± 22	89 ± 21	85 ± 16
PCWP (mm Hg)								
Control	10 ± 3	9 ± 3	8 ± 4	12 ± 4	11 ± 3	10 ± 6	6 ± 3	8 ± 3
Esmolol	13 ± 4	11 ± 3	9 ± 2	14 ± 5	11 ± 5	12 ± 3	9 ± 2	9 ± 3
CI ($L \cdot min^{-1} \cdot m^{-2}$)								
Control	2.3 ± 0.4	2.8 ± 0.6	2.8 ± 0.7	2.7 ± 0.7	2.8 ± 0.8	2.1 ± 0.4	2.1 ± 0.6	2.2 ± 0.5
Esmolol	2.3 ± 0.3	2.7 ± 0.6	2.8 ± 0.6	2.6 ± 0.6	3.0 ± 0.8	2.2 ± 0.5	1.9 ± 0.5	1.9 ± 0.5
SVR ($dynes \cdot sec^{-1} \cdot cm^{-5}$)								
Control	1580 ± 346	1194 ± 303	1175 ± 379	1699 ± 499	1578 ± 484	1952 ± 468	2026 ± 716	1812 ± 679
Esmolol	1500 ± 374	1168 ± 416	1128 ± 311	1739 ± 646	1432 ± 614	1695 ± 420	2050 ± 676	1830 ± 615
LVSWI ($g \cdot m \cdot m^{-2}$)								
Control	44 ± 9	36 ± 7	51 ± 1	44 ± 11	47 ± 14	44 ± 10	36 ± 10	37 ± 10
Esmolol	45 ± 11	33 ± 7	39 ± 12	41 ± 11	47 ± 9	37 ± 9	32 ± 11	31 ± 9

Values are mean ± SD.

Abbreviations: HR, heart rate; SAP, systolic arterial pressure; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; SVR, systemic vascular resistance; LVSWI, left ventricular stroke work index.

[a] $P = 0.0178$.

The hemodynamic data are presented in Table 4 and Figure 1. Only at 5 min after maximal sternal spread was the systemic mean arterial pressure significantly lower in the esmolol group than in the controls. At all other intervals there was no significant difference between the groups.

Four patients in the control group and three patients in the esmolol group had an ischemic episode as evidenced by ST segment changes and/or increases in PAD. The difference in incidence between groups is not statistically significant. More patients in the control group needed SNP to control the SAP than in the esmolol group. The amount of SNP administered, expressed as the integral of the SNP dose–time curve, was 11.3 ± 14.2 μg/kg in the control group and 3.1 ± 5.4 μg/kg in the esmolol treated group. This difference is statistically significant ($P = 0.02$). The steady state esmolol blood concentration in the esmolol group was 2.53 ± 0.64 μg/ml (mean ± SD). The CK-MB levels were not different between groups.

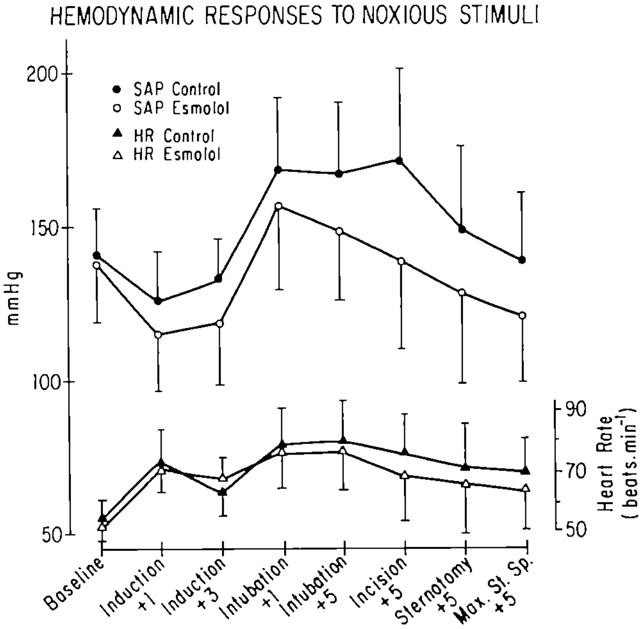

Figure 1. Hemodynamic responses to noxious stimulation (Mean ± SD). Abbreviations: HR, heart rate; SAP, systolic arterial pressure; Max.St.Sp., maximal sternal spread.

Discussion

The hemodynamic effects of esmolol in patients undergoing coronary artery surgery have recently been studied by Menkhaus et al. (2) and by Newsome et al. (7), each using a similar group of patients but a different anesthetic technique. Both groups of investigators found esmolol to be safe during anesthesia in patients with normal ventricular function and found the drug effective in attenuating the potentially harmful hemodynamic responses to noxious stimulation. Menkhaus et al. used three different doses of esmolol and all three doses of esmolol significantly attenuated the heart rate response to tracheal intubation. Rate–pressure products were lower in the esmolol-treated patients than in the controls (patients anesthetized with diazepam, pancuronium, and nitrous oxide) after intubation. Newsome et al. withheld chronic antianginal therapy in their esmolol and placebo groups but continued antianginal medication on the morning of surgery in their "standard" group, which received neither esmolol nor placebo. Esmolol patients anesthetized with fentanyl (50 μg/kg) and pancuronium had no changes in heart rate throughout the study in contrast to the control and "standard" groups in which there were significant increases in heart rate. These authors also reported an increase in pulmonary capillary wedge pressure (PCWP) in their esmolol-treated patients. They attributed this increase to myocardial depression caused by esmolol although they did not measure any direct index of myocardial performance.

Our study differs in an important aspect from both previously mentioned studies in that our patients were maintained on their regular morning dose of β-blockers (and other antianginal therapy). These patients were receiving doses adjusted by their cardiologist to produce appropriate β-adrenergic blockade. The efficacy of continued chronic β-blockade in attenuation of hemodynamic responses to noxious stimuli has been well documented. Sill et al. (8) reported an inverse correlation between log serum propranolol levels and mean arterial pressure (MAP), PCWP, cardiac index (CI), and HR responses to noxious stimulation. Kopriva et al. (9) showed that patients on chronic propranolol therapy had an attenuated HR response to intubation. Stanley et al. (10) found a decrease in narcotic requirements in CABG patients on chronic β-blocker therapy. The efficacy of continued "chronic" β-blockade is inferred from this study. We found no significant differences (with the exception of a lower MAP at 5 min after maximal sternal spread) in any hemodynamic parameter at any time during the study, between the esmolol-treated and the non-esmolol groups. As far as blood pressure measurements are concerned this finding is, of course, largely invalidated by our decision to use SNP to control SAP within certain limits, out of concern for unacceptable hypertension. The fact that the incidence of the use of SNP was significantly greater in the control group probably means that there was a significantly lower blood pressure in the esmolol-treated group. This lower blood pressure, in the absence of changes in systemic vascular resistance and CI, HR, and PCWP, points toward a decrease in myocardial contractility as the cause, and suggests that addition of esmolol to the chronically used β-blockers added an additional negative inotropic effect. A possible reason for the lack of further attenuation of the HR response to stimulation in our patients is that esmolol, in the dose employed, does not occupy sufficient additional β-receptors to produce enhanced β-adrenergic blockade. The steady state blood concentrations of esmolol in our patients were 2.53 μg/ml, which is very close to the group 2 patients who showed a steady state blood concentration of 2.36 μg/ml in the study by Menkhaus et al. These esmolol concentrations are considered to be in the therapeutic range. Patients in the study by Menkhaus et al. with a very similar anesthetic technique but with chronic β-blocker medication not continued until the time of surgery, showed an attenuated HR response to tracheal intubation, in contrast to our chronically β-blocked patients. We chose to use a diazepam-based anesthetic technique like Menkhaus et al. because it was likely that a hemodynamic response to stimulation would be seen (2), but added a low concentration of enflurane (0.9%) because we wanted to prevent very great heart rate and blood pressure increases in these patients with coronary artery disease.

In conclusion, we have shown that in patients with normal global ventricular function, maintained on their regular β-blocker until the time of surgery, esmolol does not further attenuate the heart rate response to noxious stimulation. However, esmolol did lower the blood pressure increase in these patients, probably via its negative inotropic effect. Thus, the use of esmolol would be more appropriate in patients who are not on chronic β-adrenergic blocker therapy or possibly in patients with depressed myocardial function in whom the evanescent action of esmolol might be of benefit.

References

1. Zaroslinski J, Borgman RJ, O'Donnell JP, et al. Ultra short acting beta blockers: a proposal for treatment of the critically ill patient. Life Sci 1982;31:899–907.
2. Menkhaus PG, Reves JG, Kissin I, et al. Cardiovascular effects of esmolol in anesthetized humans. Anesth Analg 1985;64:327–34.
3. Russell WJ, Morris RG, Frewin DB, Drew SE. Changes in plasma catecholamine concentrations during endotracheal intubation. Br J Anaesth 1981;53:837–9.
4. Cork RC, Weiss JL, Hameroff SR, Bentley J. Fentanyl preloading for rapid-sequence induction of anesthesia. Anesth Analg 1984;63:60–4.
5. Prys-Roberts C, Greene LT, Meloche R, Foëx P. Studies of anaesthesia in relation to hypertension. II: Haemodynamic consequences of induction and endotracheal intubation. Br J Anaesth 1971;43:531–47.
6. Stoelting RK. Circulatory changes during direct laryngoscopy and tracheal intubation: influence of duration of laryngoscopy with or without prior lidocaine. Anesthesiology 1977;47:381–4.
7. Newsome LR, Rosh JV, Hug CC, Jr, Nagle D. Esmolol attenuates hemodynamic responses during fentanyl–pancuronium anesthesia for aortocoronary bypass surgery. Anesth Analg 1986;65:451–56.
8. Sill JC, Nugent M, Muyer TP, Torres LE, Schaff HV, Tinker JH. Influence of propranolol plasma levels on hemodynamics during coronary artery bypass surgery. Anesthesiology 1984;60:453–63.
9. Kopriva CJ, Brown AD, Pappas G. Hemodynamics during general anesthesia in patients receiving propranolol. Anesthesiology 1978;48:28–33.
10. Stanley TH, de Lange S, Boscoe MJ, de Bruijn NP. The influence of chronic pre-operative propranolol therapy on cardiovascular dynamics and narcotic requirements during operation in patients with coronary artery disease. Can Anaesth Soc J 1982;29:319–24.

Pain Relief after Major Abdominal Surgery:

A Double-Blind Controlled Comparison of Sublingual Buprenorphine, Intramuscular Buprenorphine, and Intramuscular Meperidine

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CARL P, CRAWFORD ME, MADSEN NBB, RAVLO O, BACH V, LARSEN AI. Pain relief after major abdominal surgery: a double-blind controlled comparison between sublingual buprenorphine, intramuscular buprenorphine, and intramuscular meperidine. Anesth Analg 1987;66:142–6.

In a double-blind randomized study of three groups of 18 patients scheduled for major abdominal surgery the efficacy and side effects of sublingual buprenorphine were tested and compared to intramuscular meperidine and buprenorphine. Single doses of either 75 mg of meperidine, 0.4 mg of sublingual buprenorphine, or 0.3 mg of intramuscular buprenorphine were used. Patients given buprenorphine as sublingual tablets were significantly more conscious in the immediate postoperative period (Glasgow Coma Scale) than when given buprenorphine or meperidine intramuscularly. Median pain intensity differences (PID) showed equal pain relief, whereas the summarized pain intensity differences (SPID) were significantly higher in the intramuscular buprenorphine group compared to the meperidine group. Three cases of respiratory acidosis in the meperidine group required IPPV treatment, and one case in the intramuscular buprenorphine group required treatment. Sedation and nausea were the most common side effects in all three groups. We conclude that sublingual buprenorphine is useful for relief of postoperative pain and exhibited administrative advantages, when the patients were able to cooperate.

Key Words: ANALGESICS—meperidine, buprenorphine. ANALGESIA—measurement, postoperative. PAIN—postoperative.

Buprenorphine, an analogue of diprenorphine, is a relatively new synthetic opiate analgesic of high potency with mixed agonist—antagonist properties. It provides postoperative analgesia for 8–12 hr after intramuscular and intravenous administration (1,2). Sublingual administration of buprenorphine has also been used for treatment of postoperative pain and the suitability of the drug for this route is suggested by its high lipophilicity, high first pass effect, long duration of action and low addiction potential (3).

The aim of this study was to evaluate the efficacy and side effects of sublingual buprenorphine as compared to intramuscular meperidine and intramuscular buprenorphine for relief of postoperative pain.

Methods

Fifty-four patients scheduled for elective major upper abdominal surgery were randomly allocated to three equal groups in a double blind study. The trial was conducted in accordance with the Helsinki II Declaration and approved by our local Ethics Committee. Informed consent was obtained from each patient before anesthesia. Lower age limit for taking part in the study was 16 yr, but there was no upper age limit nor ASA limitation as long as there were no contraindications with regard to the anesthetic technique or postoperative narcotic analgesic medication. Excluded from the study were also patients with chronic use of analgesics, benzodiazepines, or alcohol.

Premedication consisted of diazepam, 0.2 mg/kg intramuscularly, 1 hr preoperatively. Anesthesia was induced with thiopental, 5 mg/kg intravenously, and maintained with halothane, 0.2–2%, and nitrous oxide, 67%, in oxygen. Pancuronium, 0.1 mg/kg intravenously, was used for muscle relaxation.

The first dose of analgesic was given approximately 30 min before termination of surgery. At this time

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Table 1. Preoperative Respiratory Parameters

	Intramuscular meperidine (n = 18)	Sublingual buprenorphine (n = 18)	Intramuscular buprenorphine (n = 18)
FVC (L)	3.2 (1.0–5.1)	2.9 (1.2–4.2)	3.6 (1.8–5.5)
FEV_1 (L)	2.1 (1.0–3.3)	2.1 (0.5–3.3)	2.4 (1.3–4.5)
Peak flow (L/min)	355 (60–620)	378 (125–600)	390 (140–625)
Abnormal chest x-ray	1	1	1

Values are median, range in parentheses.

Abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume.

Table 2. Quality and Duration of Pain Relief

	Intramuscular meperidine (n = 18)	Sublingual buprenorphine (n = 18)	Intramuscular buprenorphine (n = 18)
Total median duration of analgesia (hr)	6.1^a (2.3–12.5)	8.2 (2.6–12.5)	11.0^a (5–25)
PID	2.0 (0–3)	2.0 (0–3)	2.0 (0–2)
SPID	7.8^a (0.4–24.0)	9.9 (2.8–24.0)	13.6^a (6.8–48.0)

Values are median, range in parentheses.

Abbreviations: PID, pain intensity difference; SPID, sum of pain intensity difference score.

$^aP < 0.05$.

patients in group 1 double blindly received an intramuscular injection of meperidine of 75 mg plus two placebo sublingual tablets, group 2 received 1 ml of normal saline intramuscularly plus two buprenorphine sublingual tablets, i.e., 0.4 mg of buprenorphine sublingually, and finally, patients in group 3 were given 0.3 mg of buprenorphine intramuscularly plus two placebo sublingual tablets. Meperidine was compared to buprenorphine because it was the drug of choice for postoperative pain treatment in most departments. Postoperatively, analgesic medication was continued in the same manner with coded ampules and sublingual tablets. All anesthetists and recovery unit nurses supervised all patients to assure tablets were, in fact, absorbed sublingually.

Pain intensity was assessed by the patient on a 0–4 rank scale (0, no pain; 1, mild pain; 2, moderate pain; 3, severe pain; 4, intolerable pain) before and every half hour after each analgesic medication. Whenever pain intensity exceeded one point, analgesic medication was repeated. The total period of controlled analgesic treatment was 24 hr. The reduction in pain score at each observation time of administration of analgesics was calculated as the pain intensity difference (PID). The sum of pain intensity difference scores (SPID) was calculated by adding the product of each PID value and the time interval since the previous observation (4).

Arterial blood pressure, heart rate, and respiratory rate were measured each hour and immediately before medication. Arterial blood gas tensions were analyzed 60 min after medication.

The degree of consciousness was registered every half hour for 180 min by means of a modified Glasgow Coma Scale (5). This scale was considered appropriate because it is one of the few scales for estimating the general functional condition of the cerebrum, i.e., equivalent to direct assessment of the degree of sedation by means of eye reactions as well as verbal and other motor reactions. Evaluation of the latter function was modified in order to minimize various degrees of brain stem effects, as opposed to cerebral effects. Minimum and maximum values on the scale are 0 and 10 points, respectively.

On preoperative evaluation, the forced vital capacity (FVC), forced expiratory volume (FEV_1), and peak flow (PF) were measured. Chest x-rays were taken preoperatively and together with PF, were repeated 24 hr postoperatively.

All subjective and objective side effects were recorded and 24 hr after termination of anesthesia all patients were interviewed in order to calculate duration of amnesia, to record any previously unnoticed symptoms, and to record the patients point of view concerning anesthesia and pain treatment.

Statistical analysis was performed utilizing χ^2 test, Mann–Whitney rank sum test, Kruscal–Wallis test, and Dunns multiple comparisons using Kruscal–Wallis tests. Significance was assigned at 0.05.

Results

There were no significant differences in age among the three groups (medians: 58 yr, 52 yr, and 55 yr), weight (medians: 74 kg, 69 kg, and 74 kg) and ASA grouping. Duration of anesthesia (medians: 145 min, 130 min, and 144 min), blood loss, heart rate, and blood pressure intraoperatively were similar in the three groups. Table 1 shows preoperative respiratory parameters. There were no significant differences between the groups, but one patient from each group had an abnormal preoperative chest x-ray.

Postoperatively the differences in the degree of consciousness between the sublingual buprenorphine group and the other two groups were significant. The median score in group 2 30 min after termination of

Table 3. Postoperative Data

	Intramuscular meperidine (n = 18)	Sublingual buprenorphine (n = 18)	Intramuscular buprenorphine (n = 18)
Peak flow at 24 hr (L/min)[a]	252 (60–410)	256 (50–600)	270 (100–550)
Severity of changes in chest x-rays (number)			
+	1	0	1
+ +	5	5	3
+ + +	0	0	1
Cases of respiratory acidosis	5	3	2
IPPV treatment (number)	3	0	1

Abbreviation: IPPV, intermittent positive pressure ventilation.

[a] Values are median, range in parentheses.

Table 4. Number and Percentage of Patients with Side Effects during the Observation Period

	Intramuscular meperidine (n = 18)	Sublingual buprenorphine (n = 18)	Intramuscular buprenorphine (n = 18)
Sedation	12 (66%)	9 (53%)	13 (72%)
Sweating	2 (11%)	1 (6%)	1 (6%)
Nausea	11 (61%)[a]	9 (53%)	6 (33%)[a]
Vomiting	2 (11%)	2 (11%)	2 (11%)
Headache	1 (6%)	3 (18%)	0 (0%)
Dizziness	1 (6%)	2 (11%)	0 (0%)
Urinary retention	1 (6%)	0 (0%)	0 (0%)
Total number with side effects	17 (94%)[b]	13 (72%)	13 (72%)[b]

[a] $P < 0.05$.

[b] $P < 0.02$.

surgery was 9.0, after 60 min 9.5, and 10.0 after 180 min, whereas the values in group 1 were 5.5, 6.0 and 9.0, and in group 3 6.0, 8.0 and 9.5. Patients were significantly more conscious when given sublingual buprenorphine in the first hour postoperatively than when given intramuscular buprenorphine or intramuscular meperidine ($P < 0.05$ after 30 and 60 min).

The median PID values showed equal pain relief in the three groups (Table 2). On the other hand, the median SPID values were significantly higher in the intramuscular buprenorphine group (13.6) compared to the intramuscular meperidine group (7.8) ($P < 0.05$). No significant differences existed between the intramuscular meperidine group and the sublingual buprenorphine group or between the intramuscular buprenorphine group and the sublingual buprenorphine group. Duration of analgesia (Table 2) showed the same significant differences as SPID.

The total median consumption of meperidine during the 24-hr period was 337.5 mg (range 150–600 mg) given as 4.5 injections (range 2–8). In the intramuscular buprenorphine group the median dose was 0.9 mg (range 0.3–1.5 mg) given as three injections (range 1–5), whereas the sublingually administered median dose of buprenorphine was 1.6 mg (range 0.8–3.2 mg) given as eight tablets (range 4–16). There was a statistically significant difference between the median dose of intramuscular buprenorphine and buprenorphine given sublingually ($P < 0.01$).

Postoperative respiratory parameters are shown in Table 3. Five patients in group 1, five patients in group 2 and four patients in group 3 showed severely abnormal chest x-rays. In the meperidine group, five patients suffered from respiratory acidosis ($Pa_{CO_2} >$ 46 mm Hg). Three of these patients had low FEV_1 and PF values preoperatively (Table 1). Three patients were ventilated mechanically for several hours. In the sublingual buprenorphine group, three patients had respiratory acidosis and all of these patients had low FEV_1 and PF values preoperatively. In the intramuscular buprenorphine group one patient was ventilated mechanically for several hours. Only two patients had respiratory acidosis, and one of these had low respiratory parameters preoperatively. There were no significant differences between the groups with regard to abnormal chest x-rays, respiratory acidosis, and IPPV treatment. The PF values were equally reduced below preoperative values in all three groups.

Sedation (patients' opinion) and nausea were common in all three groups (Table 4). Significant difference concerning nausea was found between the meperidine group and the intramuscular buprenorphine group ($P < 0.05$).

There were no differences in duration of amnesia (7.6 hr, 5.3 hr, and 9.5 hr in groups 1, 2, and 3). One patient in group 2 and two patients in group 1 were not satisfied with pain treatment; all patients in group 3 were satisfied with pain treatment.

Discussion

The aim of the study was to evaluate the usefulness of sublingual buprenorphine compared to meperidine and buprenorphine administered intramuscularly. Sublingual administration is well recognized for treatment of angina with nitroglycerin. The route appears to have advantages not only in terms of efficiency, but also convenience, cost, and safety (6). Several investigators have used buprenorphine sublingually (7–14). Bullingham et al. found that the absolute systemic availability of 0.4 mg and 0.8 mg was approximately 56%. For both of the mentioned doses, significant plasma drug concentrations were seen at times beyond 30 min. This correlates with the time of onset of analgesia when sublingual buprenorphine was administered after a preceding intravenous dose of buprenorphine, reported as 15–45 min (8). Plasma drug concentrations of buprenorphine after sublingual administration changed relatively slowly; typically the highest drug concentrations were not reached until 3 hr after administration. This suggests that plasma drug concentrations as low as 0.4–0.6 ng/ml are associated with appreciable analgesic effect. The surprising analgesic efficacy, despite low plasma levels, of the sublingual route may be explained by the dose–plasma level response relation with respect to the sublingual route, and by specific features of buprenorphine (8). Buprenorphine is very lipophilic and its association with opiate receptors is relatively slow, but avid (15).

In our study, where the pharmacokinetic properties of buprenorphine were not studied, the indirect evidence of onset of analgesia and analgesic effect was PID, SPID, and duration of action. Compared to intramuscular administration of meperidine, with onset of analgesia after about 15 min, PID values of 2.0 for both sublingual buprenorphine and meperidine confirm that sublingual absorption is rapid even with a relatively low dose of 0.4 mg buprenorphine. The difference in duration of action between sublingually and intramuscularly administered buprenorphine corresponds to extraction ratios of 56% and 85% of the administered dose found by Bullingham et al. (7,8,9).

In this study, the consumption of buprenorphine sublingually (1.6 mg) was double the dose found by Shah et al. (14), but the same as found by Ellis et al. (11) and Derbyshire et al. (12). In one of these studies (14) the analgesics were given on patient demand, whereas in the others they were administered every 6 hr. In our study the administration of analgesics could almost be considered as on demand. Thus, the difference from the results of Shah et al. (14) is not merely explained by higher doses when the drug was administered regularly rather than on demand. However, the type of surgery might have influenced these differences because our patients were all subject to extensive surgery.

The duration of analgesia was 8.2 hr in the sublingual buprenorphine group and 11 hr in the intramuscular buprenorphine group. These results are comparable to the results of Shah et al. (14).

In the sublingual buprenorphine group the administration of the analgesic proved to be a problem during anesthesia because of the absence of salivation. However, all sublingual tablets were dissolved when a few drops of normal saline were instilled sublingually. This has also been observed by Fry (10).

The differences in level of consciousness (Glasgow Coma Scale) in our three groups of patients during the immediate postoperative period are most likely related to the slow increase of plasma concentration of buprenorphine after sublingual administration. Almost all of the patients in the meperidine group (94%) claimed unwanted side effects compared to patients treated with buprenorphine (72%). Most patients complained of nausea and sedation, a result comparable to other studies (11–14,16). In the study by Shah et al. (14) almost 60% of patients in the sublingual buprenorphine group and 80% in the intramuscular group were medicated with antiemetics. In this study the number of patients given antiemetics was not recorded. Dizziness is also a well-known unwanted side effect of buprenorphine. Edge et al. (3) claims that this symptom is proportional to the dose of buprenorphine. We recorded only two cases of dizziness in the sublingual buprenorphine group.

We conclude that sublingual buprenorphine is useful for relief of postoperative pain. Buprenorphine given sublingually exhibited administrative advantages, but in the immediate postoperative period administration of the drug sublingually may be difficult because of the inability of many patients to cooperate. This problem could be overcome by giving the drug intravenously or intramuscularly until the patients are conscious enough to cooperate.

References

1. Kay B. A double blind comparison of morphine and buprenorphine in the prevention of pain after operation. Br J Anaesth 1978;50:605–9.
2. Howell B. Comparison of buprenorphine, pethidine and pentazocine for the relief of pain after operation. Br J Anaesth 1977;49:913–5.
3. Edge WG, Cooper GM, Morgan M. Analgesic effect of sublingual buprenorphine. Anaesthesia 1979;34:463–72.
4. Manson AHB. Sublingual buprenorphine versus dihydrocodeine in postoperative pain. J Int Med Res 1981;9:506–10.
5. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. Lancet 1974;ii:81–3.
6. Dearden JC, Tomlinson E. A new buccal absorption model. J Pharm Pharmacol 1971;23:68–72.
7. Bullingham RES, Mc Quay HJ, Moore RA, Bennett MRD. Buprenorphine kinetics. Clin Pharmacol Ther 1980;28:662–72.
8. Bullingham RES, Mc Quay HJ, Dwyer D, Allen MC, Moore RA. Sublingual buprenorphine used postoperatively: clinical observations in preliminary pharmacokinetic analysis. Br J Clin Pharmacol 1981;12:117–22.
9. Bullingham RES, Mc Quay HJ, Porter EJB, Allen MC, Moore

ANESTH ANALG
1987;66:147–53

Hepatic Dysfunction after Isoflurane Anesthesia

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STOELTING RK, BLITT CD, COHEN PJ, MERIN RG. Hepatic dysfunction after isoflurane anesthesia. Anesth Analg 1987;66:147–53.

Four members of the Anesthetic and Life Support Advisory Committee of the Food and Drug Administration assessed the contribution of isoflurane (Forane®) to 45 instances of hepatic dysfunction after isoflurane anesthesia reported to the FDA for 1981–1984. For 29 (64%) of the cases, at least three members concluded that nonanesthetic causes (e.g., hypoxia, sepsis, viral infection) explained the hepatic injury. For 16 cases (36%), two or more members concluded that isoflurane might be one of several possible causes of the hepatic injury. In the latter cases, patients tended to be younger, had undergone anesthesia of shorter duration for operations outside the chest and abdomen, had developed symptoms later, had higher plasma transaminase values but lower bilirubin values, and had a lower incidence of eosinophilia, anemia, transfusions, and congestive heart failure. The committee concluded that current evidence does not indicate a reasonable likelihood of an association between the use of isoflurane and the occurrence of postoperative hepatic dysfunction.

Key Words: ANESTHETICS, VOLATILE—isoflurane. LIVER—isoflurane effects.

Isoflurane is a volatile inhalation anesthetic that was approved for clinical use in 1980. Extensive animal and clinical trials produced no evidence of hepatic dysfunction caused by isoflurane (1). The absence of a relationship between this agent and hepatic injury was ascribed to the chemical stability of isoflurane and the rapidity with which it was eliminated after anesthesia. Rapid elimination resulted from its modest blood and tissue solubility. Metabolism of isoflurane was slight. Only 0.17% of an absorbed dose of isoflurane was recovered in the form of metabolites in urine, and the latter were not considered to be hepatotoxic (2).

Despite these favorable characteristics, 45 reports of postoperative hepatic dysfunction in patients given isoflurane were filed with the Food and Drug Administration for anesthetics administered from 1981 through 1984. A subcommittee of four members of the Anesthetic and Life Support Advisory Committee of the FDA evaluated these adverse drug reports to determine if a causal association exists between administration of isoflurane and subsequent hepatic dysfunction. This report presents the findings leading to the Committee's conclusion that the current evidence does not demonstrate a causal relationship between exposure to isoflurane and hepatic dysfunction.

Methods

Each subcommittee member (RKS, CDB, PJC, RGM) independently evaluated the 45 reports of hepatic dysfunction after anesthesia with isoflurane. The information available included a single-page adverse drug report form submitted to the FDA, correspondence with physicians attending the subject patients, and an extensive summary and critique of the patient's medical history and perioperative course prepared by Edmond I. Eger II, MD. Dr. Eger is a consultant to Anaquest, the manufacturer of isoflurane (Forane®). The attending physicians included anesthesiologists, gastroenterologists, hepatologists, internists, and surgeons. These physicians received a copy of Dr. Eger's summary concerning their patient and were asked to comment on the accuracy and interpretation of the report. Their responses were also included in the reviewed material.

A list of perioperative factors that could contribute to postoperative hepatic dysfunction was assembled by the subcommittee. These included the possibility of hepatocyte hypoxia, cholestasis, viral infection, sepsis, cholangitis, administration of hepatotoxic drugs, fatty hepatic necrosis of pregnancy, and preoperative liver disease. The subcommittee also assessed whether hepatic injury occurred too long after surgery (i.e.,

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Received from the Department of Anesthesia, Indiana University School of Medicine, Indianapolis, Indiana; Old Pueblo Anesthesia, Ltd., Tucson, Arizona; the Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; and the University of Texas Health Science Center at Houston, Houston, Texas. Accepted for publication September 2, 1986.

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more than 2 weeks) to be associated with the administration of the anesthetic. Using these guidelines, each evaluator independently reached one of four conclusions regarding the role of isoflurane in causing hepatic dysfunction: not related, possibly related-unlikely, possibly related-likely, or related. The "not related" diagnosis was selected when an obvious cause for hepatic injury was present and could readily explain the degree of injury described. The remaining diagnoses were selected when a cause for hepatic injury other than isoflurane did not appear to be sufficient to explain the injury. As such, the diagnosis of isoflurane-induced hepatic dysfunction became one of exclusion.

Individual cases were then grouped according to the number of committee members who concluded that the use of isoflurane was unrelated to the occurrence of hepatic dysfunction. In group A, all four committee members agreed that no relationship existed; in group B, three of the four members agreed that no relationship existed; in group C, two of the four members agreed; in group D, only one member decided that no relationship existed; and in group E, all four members concluded that a relationship might have existed. Data for groups A through E were then compared by means of analysis of variance or χ^2 analysis to determine whether patient characteristics changed as more committee members agreed that isoflurane might have caused the dysfunction (Table 1). A total of 55 comparisons were made. In some cases we applied a logarithmic transformation to the data because of the skewed nature of particular results (e.g., transaminase). In addition, we applied regression analysis where inspection suggested a trend for any characteristic from Group A to E.

Data for groups also were combined and then compared to determine whether pooling the data displayed in Table 1 would demonstrate differences (3). Results for group A were compared to the pooled results for groups B–E; results for groups A and B were combined and compared to the pooled results on groups C–E; and the combined results for groups A and B were compared with the combined results for groups D and E (Table 2). Comparisons were made using Student's t-test, Fisher's exact test, or Pearson's χ^2 test as appropriate.

Finally, a syndrome score was computed for each patient. Syndrome components were derived from suggestions made by Lewis et al. (4) and from those of H. J. Zimmerman (personal communication to E. I. Eger), described previously (5). The score consisted of twelve variables (Table 3) graded as present (positive) or absent. For each patient, the total number of positive variables was divided by the total number of variables for which data were available. Group means and standard deviations were then calculated (Table 2).

In order to avoid a type 2 error (false negative result), no allowance was made for multiple comparisons. For all comparisons, a value of $P < 0.05$ was considered statistically significant.

Results

Several characteristics were common to almost all patients. All had surgery with an anesthetic that included isoflurane and nitrous oxide. Most also received a barbiturate and an opioid as components of their anesthetic management. All had hepatic dysfunction after anesthesia, and in all cases the attending physician had questioned whether isoflurane might have contributed to the dysfunction.

For 18 of the 45 cases (40%) postoperative hepatic dysfunction was considered as not related to isoflurane by all four reviewers (group A). For 11 additional patients (24%), hepatic dysfunction was judged not related by three reviewers and as possibly related-unlikely by one reviewer (group B). Thus, 29 of the 45 cases (64%) were judged by at least three of four reviewers to be the result of causes other than isoflurane.

In the remaining 16 cases (36%), two or more reviewers determined that isoflurane could not be excluded as a cause of postoperative hepatic dysfunction. Five were judged not related by two reviewers (group C), and eight were judged not related by one reviewer (group D). Of the three remaining cases (group E), one was judged possibly related-unlikely by three reviewers and possibly related-likely by one reviewer, and all four reviewers concluded that the other two cases were possibly related-unlikely. The latter two involved pregnant women undergoing cholecystectomy who also were treated with a β_2-adrenergic agonist (terbutaline and/or ritodrine). No reviewer invoked the related conclusion for any case.

As indicated above, there appeared to be reasonable agreement among the reviewers. All four agreed completely for 47% of the cases, and three of four reviewers agreed for an additional 40% of the cases. In only 11% of the cases was the opinion equally divided between not related and possibly related. However, a generalized κ value of 0.34 was obtained for the four reviewers suggesting, in fact, poor agreement beyond chance (6).

Because 55 variables were compared (Table 1), significant differences ($P < 0.05$) should have occurred by chance alone for three variables. In fact, five significant differences arose: time to onset of jaundice

Table 1. Analysis of Patients Grouped by Increased Suspicion of a Relationship between Administration of Isoflurane and Subsequent Hepatic Injury[a]

Variable[b]	Group A	Group B	Group C	Group D	Group E	P value
Total numbers per group	18	11	[illegible]	8	3	
Patient Age (yr)	51 ± 4 (18)	47 ± 5 (11)	48 ± 13 (5)	39 ± 6 (8)	27 ± 13 (3)	0.28
Percentage males	61 (18)	46 (11)	20 (5)	50 (8)	33 (3)	0.54
Minutes of anesthesia	215 ± 42 (18)	209 ± 57 (11)	130 ± 54 (4)	119 ± 17 (8)	143 ± 51 (3)	0.92
Log minutes of anesthesia	2.2 ± 0.4 (18)	2.2 ± 0.4 (11)	2.0 ± 0.4 (4)	2.0 ± 0.2 (8)	2.1 ± 0.4 (3)	0.76
Percentage given an opioid	88 (16)	80 (10)	100 (4)	100 (7)	100 (3)	0.60
Percentage of atopic patients	41 (17)	46 (11)	[illegible] (4)	39 (7)	0 (3)	0.31
Percentage previously given a halogenated anesthetic	46 (13)	38 (8)	50 (4)	67 (6)	— (0)	0.75
Days to symptom onset (first exposure to halogenated anesthetic)	2.5 ± 1.6 (11)	9.5 ± 10.7 (8)	5.7 ± 1.6 (3)	6.2 ± 9.9 (4)	3.0 ± 1.0 (3)	0.28
Log days to onset	0.3 ± 0.1 (11)	0.7 ± 0.2 (8)	0.8 ± 0.1 (3)	0.4 ± 0.3 (4)	0.5 ± 0.1 (3)	0.31
Days to symptom onset (multiple exposures)	6.0 ± 5.0 (4)	2.5 ± 1.3 (3)	11.5 ± 10.5 (2)	5.8 ± 1.5 (4)	— (0)	0.67
Log days to onset	0.5 ± 0.4 (3)	0.3 ± 0.2 (3)	0.7 ± 0.7 (2)	0.7 ± 0.1 (4)	— (0)	0.75
Percentage with fever as presenting symptom	40 (15)	56 (9)	[illegible] (4)	75 (8)	33 (3)	0.14
Peak temperature (°C)	38.9 ± 0.2 (14)	38.6 ± 0.3 (9)	37.7 ± 0.2 (3)	38.5 ± 0.2 (7)	39.5 ± 0.6 (3)	0.09
Percentage having jaundice	72 (18)	55 (11)	25 (4)	71 (7)	67 (3)	0.45
Days to onset of jaundice (first exposure)	3.9 ± 1.8 (7)	13.2 ± 6.0 (4)	— (0)	34 (1)	5.0 ± 2.0 (2)	0.02[c]
Log days to onset of jaundice	0.5 ± 0.2 (6)	1.0 ± 0.2 (4)	— (0)	1.5 (1)	0.7 ± 0.2 (2)	0.12
Days to onset of jaundice (multiple exposures)	6.8 ± 4.3 (5)	4.0 ± 1.0 (2)	3.[illegible] (1)	8.7 ± 2.7 (3)	— (0)	0.88
Log days to onset of jaundice	0.6 ± 0.3 (4)	0.6 ± 0.1 (2)	0.[illegible] (1)	0.9 ± 0.1 (3)	— (0)	0.81
Percentage with peak eosinophils > 6%	24 (17)	30 (10)	[illegible] (3)	0 (7)	0 (3)	0.37
Peak eosinophil count	4.0 ± 0.7 (17)	4.4 ± 1.8 (10)	1.7 ± 1.7 (3)	1.1 ± 0.6 (7)	2.7 ± 1.4 (3)	0.35
Log peak eosinophil count	0.6 ± 0.1 (15)	0.5 ± 0.2 (8)	0.[illegible] (1)	0.4 ± 0.1 (3)	0.6 ± 0.1 (2)	0.95
Percentage with rash	6 (17)	30 (10)	50 (4)	13 (8)	0 (2)	0.18
Percentage with chills	57 (14)	40 (10)	[illegible] (4)	43 (7)	33 (3)	0.36
Percentage with anorexia	79 (14)	82 (11)	75 (4)	75 (8)	33 (3)	0.53
Percentage with nausea	64 (14)	73 (11)	75 (4)	75 (8)	33 (3)	0.72
Percentage with diarrhea	54 (15)	30 (11)	75 (4)	29 (7)	0 (2)	0.27
Percentage with encephalopathy	50 (18)	60 (10)	25 (4)	14 (7)	100 (3)	0.14
Percentage with renal failure	11 (18)	20 (10)	50 (4)	0 (7)	33 (3)	0.22
Peak SGOT (IU)	1017 ± 781 (16)	2837 ± 2219 (11)	3967 ± 3142 (4)	420 ± 192 (8)	6678 ± 4501 (3)	0.31
Log peak SGOT	2.3 ± 0.2 (16)	2.9 ± 0.2 (11)	3.1 ± 0.4 (4)	2.4 ± 0.2 (8)	3.4 ± 0.5 (3)	0.01[c]
Percentage with peak SGOT > 370 IU	19 (16)	73 (11)	75 (4)	25 (8)	67 (3)	0.04[d]
Peak SGPT (IU)	851 ± 516 (13)	1874 ± 1190 (10)	3119 ± 1706 (4)	687 ± 316 (6)	4536 ± 2063 (3)	0.23
Log peak SGPT	2.2 ± 0.2 (13)	2.8 ± 0.2 (10)	3.3 ± 0.3 (4)	2.6 ± 0.2 (6)	3.4 ± 0.4 (3)	0.009
Peak LDH (IU)	886 ± 444 (16)	3513 ± 3064 (8)	4688 ± 4396 (3)	385 ± 1042 (7)	1847 ± 1603 (2)	0.51
Log peak LDH	2.6 ± 0.1 (16)	2.9 ± 0.2 (8)	3.0 ± 0.6 (3)	2.5 ± 0.1 (7)	3.0 ± 0.6 (2)	0.46
Peak alkaline phosphatase	299 ± 71 (16)	289 ± 45 (11)	335 ± 84 (4)	358 ± 83 (7)	296 ± 46 (3)	0.97
Log peak alkaline phosphatase	2.3 ± 0.1 (16)	2.4 ± 0.1 (11)	2.5 ± 0.1 (4)	2.5 ± 0.1 (7)	2.5 ± 0.1 (3)	0.74
Peak bilirubin (mg/dl)	11.3 ± 2.9 (17)	6.4 ± 2.4 (11)	2.0 ± 0.4 (4)	4.2 ± 1.7 (7)	12.7 ± 8.5 (3)	0.24
Log peak bilirubin	0.8 ± 0.1 (17)	0.5 ± 0.2 (11)	0.3 ± 0.1 (4)	0.4 ± 0.2 (7)	0.6 ± 0.6 (3)	0.29
Percentage with bilirubin > 2.5 mg/dl	77 (17)	55 (11)	25 (4)	43 (7)	67 (3)	0.29
Percentage obese (> 20% above ideal Davidson Score[3])	38 (16)	36 (11)	50 (4)	38 (8)	33 (3)	0.99
Percentage with major cavity surgery	72 (18)	46 (11)	80 (5)	13 (8)	0 (3)	0.01

(continued)

Table 1. (*continued*)

Variable[b]	Group A	Group B	Group C	Group D	Group E	P value
Percentage with history of blood pressure > 140/90 mm Hg	28 (18)	30 (10)	25 (4)	13 (8)	67 (3)	0.52
Percentage with postoperative pressure decrease > 30%	44 (18)	30 (10)	50 (4)	0 (6)	67 (3)	0.23
Percentage with postoperative congestive heart failure	35 (17)	0 (10)	0 (4)	0 (8)	33 (3)	0.06
Percentage with postoperative hypoxemia	69 (13)	67 (9)	60 (5)	0 (4)	100 (2)	0.09
Lowest Pa_{O_2} (mm Hg)	58 ± 3 (8)	61 ± 5 (6)	67 ± 19 (3)	— (0)	48 ± 11 (2)	0.62
Percentage with hemoglobin < 10 g/dl	39 (18)	60 (10)	33 (3)	0 (7)	33 (3)	0.17
Lowest hemoglobin (g/dl)	10.8 ± 0.5 (17)	9.5 ± 0.7 (10)	9.7 ± 0.9 (2)	12.2 ± 0.8 (7)	12.6 ± 2.1 (3)	0.09
Percentage receiving transfusions	61 (18)	60 (10)	25 (4)	25 (8)	33 (3)	0.33
Units of blood transfused	5.8 ± 2.3 (18)	10.7 ± 7.3 (10)	1.8 ± 1.8 (4)	2.1 ± 1.9 (8)	1.3 ± 1.3 (3)	0.61
Percentage with evidence of sepsis	59 (17)	78 (9)	40 (5)	50 (6)	0 (2)	0.29
Percentage with centrilobular necrosis	14 (7)	50 (2)	0 (2)	0 (1)	— (0)	0.53
Percentage dead	35 (17)	18 (11)	40 (5)	0 (8)	50 (2)	0.28
Syndrome score	0.46 ± 0.04 (18)	0.50 ± 0.07 (11)	0.49 ± 0.13 (5)	0.42 ± 0.07 (8)	0.40 ± 0.15 (3)	0.90

[a] The lowest suspicion is for group A; the highest for group E.
[b] Values are given as the mean ± the standard error of the mean; in each set, the number in parentheses is the number of patients for that set.
[c] Significant by χ^2 analysis.
[d] Significant by analysis of variance.

after first exposure, log peak SGOT, SGOT >370 units, log peak SGPT, and major cavity surgery. No pattern emerged that would suggest a causal role for isoflurane. For example, regression analysis did not reveal a progressive change in any of the five variables as more reviewers considered that isoflurane could not be excluded as a causal factor. In addition, the changes in transaminases are not independent and may be considered to indicate a single significantly different variable. Jaundice after a first exposure to isoflurane did not occur sooner after anesthesia as the suspicion for a possible role of isoflurane increased, i.e., there was no consistent change from group A through group E.

Patients for whom a greater fraction of the reviewers (i.e., groups D and E) considered isoflurane a potential cause tended to be younger. Although the difference in age among groups was not significant according to analysis of variance (Table 1), regression analysis yielded a significant negative correlation between an increasing fraction of reviewers who considered isoflurane a potential cause and age ($r = -0.35$, $P < 0.016$). This was the only significant correlation given by regression analysis.

The comparisons between combined groups revealed a greater number of significant differences (Table 2). The differences are summarized as follows. The patient suspected of having isoflurane-induced hepatic injury: 1) was likely to be younger; 2) had a shorter duration of anesthesia; 3) was less likely to have undergone surgery in a major cavity; 4) had a longer time to onset of symptoms; 5) had a higher peak serum transaminase, but 6) lower serum bilirubin levels; and was less likely to develop 7) eosinophilia, or 8) anemia; or to have 9) a transfusion, or 10) congestive heart failure. The syndrome score was not significantly different between any combination of single or pooled groups (Tables 1 and 2).

Discussion

Perioperative hepatic injury has diverse origins. For example, the reviewers found injury possibly related to sepsis, hypoxia (including hepatic infarction), biliary obstruction, nutritional deficiency (prolonged, i.e., more than 30 days, vomiting), circulatory shock, viral hepatitis (including herpes virus), and antibiotic (erythromycin estolate) administration. The diverse causes of hepatic injury have been noted in other investigations of hepatic injury after anesthesia with a halogenated anesthetic (5,7).

Thorough investigation is required to discover the source of hepatic injury after anesthesia. One example is the finding that herpes virus caused massive he-

Table 2. Significant Differences in Patient for Combined Groups

Variable	Groups[a] compared	Values for unlikely groups[b]	Values for possible groups[b]	P value
Patient age (yr)	A and B vs D and E	49.6 ± 3.3 (29)	35.7 ± 5.2 (11)	0.04
Minutes of anesthesia	A and B vs C–E	213 ± 33 (29)	127 ± 18 (15)	0.03
Percentage having major cavity surgery	A and B vs D and E	62 (29)	9 (11)	0.004[c]
Days to symptoms (first exposure)	A vs B–E	2.46 ± 0.49 (11)	7.06 ± 1.98 (18)	0.04
Log peak SGOT	A vs B–E	2.28 ± 0.16 (16)	2.83 ± 0.13 (26)	0.01
Log peak SGPT	A and B vs C–E	2.47 ± 0.15 (23)	2.99 ± 0.18 (13)	0.04
Log peak bilirubin	A vs B–E	0.82 ± 0.13 (17)	0.45 ± 0.11 (25)	0.04
Peak eosinophil count (%)	A and B vs D and E	4.15 ± 0.79 (17)	1.60 ± 0.58 (10)	0.01
Percentage having anemia	A and B vs D and E	46 (28)	10 (10)	0.04
Lowest hemoglobin (g/dl)	A and B vs D and E	10.3 ± 0.42 (27)	12.3 ± 0.77 (10)	0.04
Percentage having transfusions	A and B vs C–E	61 (28)	27 (15)	0.04[c]
Percentage having congestive heart failure	A vs B–E	35 (17)	4 (25)	0.02[c]
Syndrome score	A vs B–E	0.46 ± 0.04 (18)	0.46 ± 0.10 (27)	NS
Syndrome score	A and B vs C–E	0.47 ± 0.04 (29)	0.44 ± 0.06 (16)	NS
Syndrome score	A and B vs D and E	0.47 ± 0.04 (29)	0.41 ± 0.06 (11)	NS

Abbreviation: NS, not significant.

[a] The first groups consist of patients whose hepatic injury was judged unlikely to be related to the administration of isoflurane by at least three of the four committee members; the second groups (B–E, C–E, or D and E) consist of patients whose hepatic injury was judged possibly related to the administration of isoflurane by one (group B) or more committee members (groups C, D, E).

[b] Values are given as the mean, ± SEM where applicable; in each set, the number in parentheses is the number of patients for that set.

[c] Significant by Fisher's exact test; otherwise, determined by χ^2 or t-test.

patic necrosis in a 62-yr-old patient for whom isoflurane had been part of the anesthetic management for cholecystectomy and removal of renal stones (8). Hepatic injury was noted before this patient died, and the attending physicians questioned whether isoflurane had contributed to the injury. However, at postmortem examination, inclusion bodies were found in the liver and electron microscopy revealed numerous viral particles. A similar case has been reported for enflurane (Ethrane) (9), a related compound.

In another case, a six-yr-old, 20.5 kg girl was given isoflurane and nitrous oxide for tonsillectomy and adenoidectomy. Vomiting, diarrhea, and abdominal pain appearing around the seventh postoperative day led to investigations on the tenth day. Bilirubinuria and increased serum transaminases (SGOT, 244 IU; SGPT, 392 IU) in the absence of positive markers of viral infection suggested that isoflurane might have caused the hepatic injury. This diagnosis was discarded when the attending pediatrician discovered that the surgeon had administered adult doses of erythromycin estolate for 2–3 days before surgery and for 7 days thereafter. Erythromycin estolate can produce nausea, vomiting, abdominal pain, and hepatic dysfunction (10).

These observations suggest that the etiology of some cases of alleged anesthetic-induced hepatitis, including several in the present series, could be resolved by a thorough evaluation. The role of isoflurane in postoperative hepatic dysfunction is more likely to be discounted when extensive laboratory tests and detailed perioperative information are available. The diagnosis of anesthetic-induced hepatic injury can be made only by exclusion of other likely causes of injury.

The reviewers concluded that causes other than isoflurane could account for postoperative hepatic dysfunction in 29 of the 45 cases of hepatic injury after anesthesia with isoflurane. Comparison of these 29 patients with the remaining 16 patients for whom isoflurane could not be excluded as a cause of postoperative hepatic dysfunction did not reveal a pattern of characteristics that distinguished the two groups.

The data did not indicate an "allergic" or "sensitization" response such as is ascribed to halothane hepatitis (7). The suspect groups (C, D, and E) did not have a higher incidence of history of allergy (21% in groups C, D, and E vs 43% in groups A plus B), history of prior exposure to a volatile anesthetic (50% vs 43%), fever as a presenting symptom (27% vs 46%); eosinophilia (0% vs 26%), or rash (21% vs 15%). Time to onset of symptoms did not shorten after multiple exposures (6.0 days after multiple exposures; 5.3 days after a first exposure). Similarly, the syndrome score was not higher in the suspect group (Tables 1, 2).

Many characteristics of the 45 patients were similar to those thought to be associated with halothane-induced hepatitis. Such characteristics were found equally in patients for whom causes other than isoflurane were apparent and in those for whom such causes were less apparent or not apparent at all (e.g., see the syndrome score comparisons in Table 2).

However, the parallels between halothane and iso-

Table 3. Syndrome Variables

Prior anesthesia with a halogenated anesthetic
Fever as a presenting sign
Chills
Nausea
Anorexia
Rash
Eosinophilia
An observation of jaundice by the attending physicians
A total bilirubin level exceeding 2.5 mg/dL
A value for serum glutamic-oxaloacetic transaminase (SGOT) above 370 IU (i.e., more than ten times the upper limit of the normal range)
The presence of centrilobular necrosis
Death of the patient

flurane that would provide a common explanation for anesthetic-induced hepatitis are limited. Although both are potent halogenated anesthetics that can produce profound cardiorespiratory depression, isoflurane differs from halothane in several ways considered important to possible anesthetic-induced hepatotoxicity. The present reports do not indicate a sensitization (i.e., an allergic hepatitis) such as that suggested for halothane. Isoflurane is stable in the presence of sunlight or soda lime (1). Metabolism of isoflurane is two orders of magnitude less than the metabolism of halothane (2,11). Unlike halothane (12,13), isoflurane does not undergo reductive metabolism (14) nor does metabolism result in the production of free radicals (15,16). Isoflurane tends to maintain hepatic blood flow, and preserve autoregulation and delivery of oxygen to the liver whereas halothane decreases blood flow and autoregulation (17–20). However, these differences between isoflurane and halothane may not be relevant if halothane hepatitis arises from other (unknown) mechanisms, mechanisms that may be shared by isoflurane. Alternatively, hepatitis after general anesthesia may be unrelated to the anesthetics given in the perioperative period.

The incidence of perioperative hepatic dysfunction from causes other than anesthesia appears to be much greater than the incidence that might be attributed to isoflurane. For example, routine performance of preoperative liver function tests in asymptomatic adult patients scheduled for elective surgery revealed unsuspected hepatic dysfunction in 1 of every 700 patients (21,22). Although no surgery was performed, jaundice subsequently developed in about a third of the patients having dysfunction. The incidence of postoperative non-A, non-B hepatitis is reportedly 3.3% in patients undergoing surgical procedures not requiring blood transfusion (23). The incidence of hepatic dysfunction that might be estimated from the 45 reports described in the present report is 0.00032% (45 reports during a period when an estimated 14 million anesthesias were conducted with isoflurane). This incidence obviously is an underestimate but does suggest the rarity of suspected cases of isoflurane hepatitis. Such a rare event may not be distinguishable from the "noise" produced by other causes of hepatic injury. The diagnosis of isoflurane-induced hepatic dysfunction may require the administration of a challenge test.

The two reports of postoperative hypatic injury in pregnant patients treated with a β_2-agonist and undergoing cholecystectomy suggest the need for careful future monitoring for this complication in such patients. A potential interaction of these events and drugs (including anesthetics) has not been previously reported. Nevertheless, it would be premature to incriminate isoflurane as a causal link in this sequence. The stress of upper abdominal surgery and chronic administration of a drug that may decrease hepatic blood flow may of themselves be sufficient causes.

In summary, the Anesthetic and Life Support Advisory Committee to the FDA concluded that these 45 reports do not reveal a reasonable association between administration of isoflurane and the subsequent appearance of hepatic dysfunction. Future reports alleging isoflurane-induced hepatic dysfunction will be evaluated by the committee using the same criteria applied to these 45 cases. The medical community and patients will be best served by this continued surveillance and by avoiding diagnoses of anesthetic-induced hepatic dysfunction that are not substantiated by extensive laboratory investigations and thorough analyses of patient medical history and perioperative course.

The authors gratefully acknowledge the comments and suggestions made by Drs. Edmond I. Eger (University of California, San Francisco), Arthur S. Keats (Texas Heart Institute), Patricia H. Russell (Division of Surgical-Dental Products, FDA), David L. Scally (Division of Surgical-Dental Products, FDA), and Leroy D. Vandam (Brigham and Women's Hospital).

References

1. Eger EI II. Isoflurane (Forane). A compendium and reference. Madison, Wisconsin: Anaquest, 1985.
2. Holaday DA, Fiserova-Bergerova V, Latto IP, et al. Resistance of isoflurane to biotransformation in man. Anesthesiology 1975;43:325–32.
3. Davidson MB. Diabetes mellitus: diagnosis and treatment. New York: John Wiley and Sons, 1981:52.
4. Lewis JH, Zimmerman HJ, Ishak KG, et al. Enflurane hepatotoxicity. A clinico-pathologic study of 24 cases. Ann Intern Med 1983;98:984–92.

5. Eger EI II, Smuckler EA, Ferrell LD, et al. Is enflurane hepatotoxic? Anesth Analg 1986;65:21–30.
6. Davies M, Fleiss JL. Measuring agreement for multinomial data. Biometrics 1982;38:1047–51.
7. Subcommittee on the National Halothane Study of the Committee on Anesthesia, National Academy of Sciences-National Research Council. Summary of the national halothane study. Possible association between halothane anesthesia and postoperative hepatic necrosis. JAMA 1966;197:775–88.
8. Fisher NA, Iwata RT, Eger EI II, et al. Hepatic necrosis associated with herpes virus after isoflurane anesthesia. Anesth Analg 1985;64:1131–3.
9. Douglas HJ, Eger EI II, Biava CG, et al. Hepatic necrosis associated with viral infection after enflurane anesthesia. N Engl J Med 1977;296:553–5.
10. McCormack WM, Donner GH, Kodgis LF, et al. Hepatotoxicity of erythromycin estolate during pregnancy. Antimicrob Agents Chemother 1977;12:630–5.
11. Rehder K, Forbes J, Alter H, et al. Halothane biotransformation in man: A quantitative study. Anesthesiology 1967;28:711–5.
12. Gourlay GK, Adams JF, Cousins MJ, et al. Genetic differences in reductive metabolism and hepatotoxicity of halothane in three rat strains. Anesthesiology 1981;55:96–103.
13. Widger LA, Gandolfi AJ, Van Dyke RA. Hypoxia and halothane metabolism in vivo: release of inorganic fluoride and halothane metabolite binding to cellular constituents. Anesthesiology 1976;44:197–201.
14. Ross WT Jr. Plasma fluoride concentration during halogenated anesthetic administration with normoxia and hypoxia. Anesthesiology 1982;57:A217.
15. Massion WH, Poyer JL, Downs P, et al. Comparative study of halogenated hydrocarbon toxicity and free radial formation in rat liver. Anesthesiology 1984;61:A274.
16. Plummer JL, Beckwith ALJ, Bastin FN, et al. Free radical formation in vivo and hepatotoxicity due to anesthesia with halothane. Anesthesiology 1982;57:160–6.
17. Gelman S, Fowler KC, Smith LR. Liver circulation and function during isoflurane and halothane anesthesia. Anesthesiology 1984;61:726–30.
18. Gelman S, Fowler KC, Smith LR. Regional blood flow during isoflurane and halothane anesthesia. Anesth Analg 1984; 63:557–65.
19. Gelman S, Rimerman V, Fowler KC, et al. The effect of halothane, isoflurane, and blood loss on hepatotoxicity and hepatic oxygen availability in phenobarbital-pretreated hypoxic rats. Anesth Analg 1984;63:965–72.
20. Ostman M, Biber B, Martner J, et al. Effects of isoflurane on vascular tone and circulatory autoregulation in the feline small intestine. Acta Anaesthesiol Scand 1985;29:389–94.
21. Schemel WH. Unexpected hepatic dysfunction found by multiple laboratory screening. Anesth Analg 1976;55:810–2.
22. Wataneeyawech M, Kelly KA Jr. Hepatic diseases unsuspected before surgery. NY State J Med 1975;75:1278–81.
23. Dienstag JL. Non-A, non-B hepatitis. I. Recognition, epidemiology, and clinical features. Gastroenterology 1983;85:439–62.

Hypertonic Saline as a Resuscitation Solution in Hemorrhagic Shock:

Effects on Extravascular Lung Water and Cardiopulmonary Function

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LAYON J, DUNCAN D, GALLAGHER TJ, BANNER MJ. Hypertonic saline as a resuscitation solution in hemorrhagic shock: effects on extravascular lung water and cardiopulmonary function. Anesth Analg 1987;66:154–8.

To determine the effect of resuscitation with hypertonic saline on extravascular lung water, seven adult sheep were endotracheally intubated; mean arterial pressure (MAP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and central venous pressure (CVP) were monitored. A 5-French, thermistor-tipped catheter was used to measure extravascular lung water (EVLW). Colloid oncotic pressure (COP), serum electrolytes and osmolality, and arterial and mixed venous blood gas tensions were measured. The COP-PCWP gradient and the shunt fraction (Q̇sp/Q̇t) were calculated. After baseline measurements, the animals were bled to an MAP of 50 mm Hg (blood volume removed, 16.2 ± 3.6 ml/kg), which was maintained for 30 min, measurements then being repeated. Three percent sodium chloride solution was infused at 500 ml/15 min until two of three parameters—cardiac output (CO), PCWP, or MAP—were restored to baseline values. Data were recorded again and then 60 min later. No shed blood was reinfused. The total volume of hypertonic saline infused was 39 ± 19 ml/kg. Pulmonary artery pressure did not vary throughout the study. PCWP, MAP, and CO were significantly lower than baseline ($P < 0.05$) 30 min after bleeding but all except MAP returned to baseline with resuscitation. Throughout the study, EVLW did not vary despite a COP-PCWP gradient less than 4 mm Hg. Serum sodium levels and serum osmolality were significantly above baseline values after resuscitation. In this animal model of hemorrhagic shock, infusion of hypertonic saline effected resuscitation without compromising cardiopulmonary function or increasing EVLW.

Key Words: SHOCK—treatment. FLUID BALANCE. LUNG—edema

Controversy about the use of colloids or crystalloids for hemorrhagic shock resuscitation has continued for at least 100 years (1,2). Several authors have recently advocated hypertonic saline solutions for resuscitation from hemorrhagic shock (3–5) and thermal injury-induced shock (6–9). The concentration of sodium in these studies has ranged between 0.9% (154 mEq/L) and 6% (1025 mEq/L).

Although noncolloid (i.e., lactated Ringer's or normal saline) solutions for resuscitation have been considered a cause of pulmonary edema, pulmonary capillary permeability has not been shown to increase with acute hemorrhagic shock (10,11). We studied the effects of hypertonic saline infusion on extravascular lung water (EVLW) in an ovine (12,13) model of hemorrhagic shock.

Materials and Methods

Seven sheep (43–75 kg) kept in a facility fully accredited by the American Association for Laboratory Animal Care were given intravenous thiamylal sodium in a single dose of 15 mg/kg to induce anesthesia; thereafter, small intravenous doses were used to maintain anesthesia. The animals were intubated by direct laryngoscopy and mechanical ventilation was initiated with a time-cycled, volume-limited ventilator at a frequency of eight breaths/min, a tidal volume of 15 ml/kg body weight at zero end-expiratory pressure, and an F_{IO_2} of 0.5. Ventilatory frequency was adjusted to keep Pa_{CO_2} between 35 and 45 mm Hg. A pulmonary artery flotation catheter (American-Edwards

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Presented in part at the annual meeting of the International Anesthesia Research Society, March 1985, Houston, Texas.

Received from the Departments of Anesthesiology, Medicine, and Surgery, University of Florida College of Medicine, Gainesville, Florida. Accepted for publication September 17, 1986.

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Table 1. Effects of Hypertonic Solution on Shock

	Before shock	30 Min after shock	Time after resuscitation	
			0	60 min
PAP (mm Hg)	19.4 ± 2.5	17.0 ± 5.9	20.0 ± 7.2	20.4 ± 6.0
PCWP (mm Hg)	13.1 ± 4.9	10.0 ± 4.6[a]	13.6 ± 4.4[b]	14.[illegible] ± 4.8[a]
MAP (mm Hg)	127.1 ± 14.8	49.3 ± 8.4[a]	110.0 ± 10.8[a]	103.6 ± 16.8[a]
CO (L/min)	5.05 ± 2.4	2.3 ± 0.8[a]	5.1 ± 1.5[b]	6.3 ± 2.4[a]

Values are means ± SD.
[a] $P < 0.05$ compared with before shock.
[b] $P < 0.05$ compared with 30 min after shock.

Corp., Irvine, CA) was placed by cutdown into the internal jugular vein and correct placement was verified by waveform tracing. Pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and central venous pressure (CVP) were monitored. A 5-French, thermistor-tipped catheter (American-Edwards Corp., Irvine, CA) was placed into the common carotid artery and used for blood pressure monitoring as well as EVLW determination by the thermal-dye technique (14). Injections for measuring CO and EVLW were always made in duplicate at end-exhalation; they were always within 10% or 50 ml of each other, respectively. Hemodynamics were measured by strain-type transducers (P23 Physiologic Pressure Transducer, Gould-Statham, Oxnard, CA). A 14-gauge bleed line was placed into the other common carotid artery. All tracings were transcribed on a calibrated paper recorder (Grass Medical Instruments, Inc., Quincy, MA). Anaerobic blood sampling was performed in each animal for measurements of colloid oncotic pressure (COP) (Wescor, Model 4100, Logan, UT), serum electrolyte levels, osmolality, and arterial and mixed venous blood gas tensions. The blood gas tensions and oxygen saturations were analyzed with an IL-1303 blood gas analyzer and IL-282 co-oximeter, respectively (Instrumentation Laboratory, Inc., Lexington, MA). The COP-PCWP gradient and shunt fraction ($\dot{Q}sp/\dot{Q}t$) were calculated. Flush solutions contained 5 U of USP beef heparin per milliliter.

After baseline measurements, animals were bled through the arterial catheter via a roller-pump (Cole-Parmer Instrument Co., Chicago, IL) at a rate of 50 ml/min to produce a mean arterial pressure (MAP) of 50 mm Hg. This pressure was maintained for 30 min, after which measurements were repeated. The animals were then infused with hypertonic saline solution (3% NaCl: 513 mEq Na, 513 mEq Cl, 1026 mOsm/L) at a rate of 500 ml/15 min until two of three parameters (CO, PCWP, or MAP) were restored to baseline values. Three percent saline solution was then infused as needed to keep those parameters at baseline values. Data were recorded again at the time of resuscitation and 60 min later. All blood gas results were temperature corrected (15). Core temperature was monitored and, when necessary, controlled via heat lamps and blankets. After all data were collected, lethal doses of intravenous potassium chloride and thiamylal sodium were administered. Baseline data were compared with data from the other time periods by an analysis of variance and, secondarily, Duncan's multiple range test. Statistical significance was designated at $P < 0.05$. All data are presented as mean ± SD.

Results

To induce shock, 16.2 ± 3.6 ml/kg of blood was removed. Throughout the study, pulmonary artery pressure did not vary (Table 1). Pulmonary capillary wedge pressure, MAP, and CO were significantly below baseline levels 30 min after blood loss; all but MAP returned to baseline values with resuscitation. Sixty minutes after resuscitation, MAP was still significantly below baseline values. Extravascular lung water did not vary throughout the study (Table 2). Colloid oncotic pressure was significantly below baseline 30 min after shock and declined even further with resuscitation. Values for COP were significantly lower after resuscitation than either at baseline or 30 min after shock. The COP-PCWP gradient declined dramatically after resuscitation; however, this was due to a decreased COP rather than to an increased PCWP. Shunt fraction increased significantly 60 min after resuscitation. Serum sodium and osmolality were significantly greater than baseline values, whereas serum potassium was markedly lower than baseline values (Table 3). The volume of hypertonic fluid required for resuscitation was 39.0 ± 19 ml/kg.

Discussion

Although the physiology of pulmonary microcirculation, interstitium, and alveoli is not well understood, any discussion of the pulmonary microcircu-

Table 2. Effects of Hypertonic Solution on Shock

	Before shock	30 Min after shock	Time after resuscitation 0	Time after resuscitation 60 Min
EVLW (ml/kg)	11.6 ± 5.8	8.8 ± 4.1	8.0 ± 3.0	9.9 ± 4.6
COP (mm Hg)	20.6 ± 1.5	16.8 ± 1.6[a]	12.0 ± 1.8[a,b]	11.5 ± 2.3[a,b]
COP-PCWP gradient	7.4 ± 6.0	6.8 ± 5.2	−1.6 ± 5.7[a,b]	−2.6 ± 6.2[a,b]
Venous admixture (%)	0.9 ± 0.6	1.1 ± 1.1	2.1 ± 2.4	4.1 ± 4.5[a,b]

Values are means ± SD.
Abbreviations: EVLW, extravascular lung water; COP, colloid oncotic pressure; PCWP, pulmonary capillary wedge pressure.
[a] $P < 0.05$ compared with before shock.
[b] $P < 0.05$ compared with 30 min after shock.

Table 3. Effect of Hypertonic Fluid on Serum Values after Shock

	Before shock	Time after resuscitation 0	Time after resuscitation 60 Min
Sodium (mEq/L)	150.8 ± 2.3	167.8 ± 9.2[a]	183.3 ± 15.4[a]
Potassium (mEq/L)	3.2 ± 0.3	2.3 ± 0.4[a]	2.6 ± 0.7[a]
Osmolality (mOsm/kg H_2O)	298.3 ± 1.4	330.8 ± 10.7	352.3 ± 21.4[a,b]

Values are means ± SD. The total volume of fluid infused after 60 min of resuscitation was 39.0 ± 19 ml/kg.
[a] $P < 0.05$ compared with before shock.
[b] $P < 0.05$ compared with 0 min after resuscitation.

lation must, of necessity, begin with Starling's equation (11), which describes fluid flux across a semipermeable membrane:

$$\dot{Q}_f = K_f\,[(P_{mv} - P_{pmv}) - \sigma(\pi_{mv} - \pi_{pmv})]$$

where $\dot{Q}_f$ is the net transvascular fluid filtration rate, K_f is the filtration coefficient, P_{mv} is the microvascular hydrostatic pressure, P_{pmv} is the (interstitial) perimicrovascular hydrostatic pressure, π_{mv} is the microvascular colloid osmotic pressure, π_{pmv} is the (interstitial) perimicrovascular colloid osmotic pressure, and σ is the protein reflection coefficient, this last being the relative permeability of the membrane to protein and ranging from 0 (total permeability) to 1 (complete impermeability). With such a substantial decrease of COP (which approximates π_{mv}) and a return of PCWP (which approximates P_{mv}) to baseline values as occurred in our study, resulting in a COP-PCWP gradient much less than 4 mm Hg after resuscitation, we might have expected $\dot{Q}_f$ and, thus, EVLW to increase. There are several explanations why this was not so.

$\dot{Q}_f$ may indeed have increased, but lung lymph flow ($\dot{Q}_L$) may have increased as well, which would have prevented an increase of EVLW (11). The sodium content of pulmonary interstitial collagen increases substantially during hemorrhagic shock and returns to normal after resuscitation (16,17). This mechanism may involve pH-related electrochemical changes that increase the availability of sodium and the affinity of collagen for the ion (17), which, in turn, may increase P_{pmv} and, thus, by creating a new equilibration of forces, oppose fluid movement into the interstitium. Also, the increase in pulmonary interstitial collagen sodium content may affect the compliance of the pulmonary interstitium when pulmonary interstitial water increases (18). This compliance change may decrease the ratio of gel to sol in the interstitium and, thus, may enhance interstitial lung water movement to the perihilar area and away from the gas-exchanging portions of the lung.

In healthy animals and humans, "edema protection factors," such as pulmonary lymph flow, low microvascular barrier liquid conductance (K_f), very low microvascular barrier protein conductance, plasma protein concentration, and perimicrovascular liquid pressure (18), act to prevent submassive, acute effects from resulting in pulmonary edema. In a compromised person only minimal perturbations in these protective factors could cause clinical pulmonary edema or a subclinical increase in EVLW that compromises pulmonary function and causes hypoxemia. This may be the heart of the COP-PCWP gradient controversy.

Clinical pulmonary edema has been observed when the COP-PCWP gradient has decreased to 4 mm Hg or less (19–22). Our study, as well as other studies (23–27), suggest that the COP-PCWP gradient may only become significant in physiologically compromised patients (i.e., those with compensated congestive cardiomyopathy). An acute event such as hemorrhage with crystalloid (either isotonic or hypertonic) replacement may result in a COP-PCWP gradient of 4 mm Hg or less and subclinical or clinical pulmonary edema.

The severe electrolyte and osmolality abnormalities probably resulted from the rapidity of the infusion; using a slower infusion rate (4) or simply changing to a less concentrated solution (lactated Ringer's or normal saline solution) when plasma sodium exceeds 160 mEq/L or plasma osmolality exceeds 340 mOsm/L (6) may prevent this. Previous work in our laboratory suggests that an isotonic resuscitation fluid will not increase EVLW accumulation (26).

Finally, hypertonic saline may increase myocardial contractility (28–30), dilate precapillary vessels, and constrict capacitance vessels (3,28). These effects, which occur at an osmolality of approximately 385–400 mOsm/kg, occur both in vitro and in vivo and persist after autonomic blockade. It is not clear how much model species (sheep vs cat vs dog) might affect these data.

The increase in shunt 60 min after resuscitation from shock was most probably due to atelectasis. Furthermore, the increased cardiac output at that time may have increased blood flow through areas of low ventilation-to-perfusion ratio and, thus, may have increased the observed shunt fraction.

In summary, 3% saline solution effectively restored hemodynamic stability in a model of hemorrhagic shock. This hypertonic crystalloid solution did not appear to increase EVLW or to compromise pulmonary function, as evidenced by normal PaO_2 and shunt fraction. A concern when using this solution has been perturbation of serum electrolytes and osmolality, which did occur in our study. However, a slower infusion may minimize these adverse effects. Although some might question the usefulness of hypertonic saline in usual clinical situations, this solution can be used to restore intravascular volume when a large volume of more dilute solutions is ill-advised. Specifically, several studies (6,8,9) have noted that, compared with the use of isotonic solutions, the use of hypertonic solutions for burn resuscitation is associated with a decrease of total water load and edema, which may result in fewer burns progressing from partial to full thickness. Thus, in our model, hypertonic saline compares favorably with an isotonic balanced saline solution in terms of resuscitation from hemorrhagic shock and effects on pulmonary function (26). Our data and those of others (6,8,9) suggest that hypertonic saline may be useful in selected situations and that this type of solution should be carefully considered for clinical use. Finally, although animal studies are not often directly applicable to humans, information gleaned from such studies makes clearer the questions that must be addressed in treating humans.

The staff of the Cardiopulmonary Laboratory of the Department of Anesthesiology assisted in the study and the editorial staff of the Department of Anesthesiology helped prepare the manuscript.

References

1. Lane WA. A surgical tribute to the late Dr. Woodridge. Lancet 1891;ii:626–7.
2. Sherrington CS, Copeman SM. Variations experimentally produced in the specific gravity of the blood. J Physiol (London) 1893;14:52–96.
3. Velasco IT, Pontieri V, Rocha E, Silva M Jr, et al. Hyperosmotic NaCl and severe hemorrhagic shock. Am J Physiol 1980;239:H664–73.
4. Nerlich M, Gunther R, Demling RH. Resuscitation from hemorrhagic shock with hypertonic saline or lactated Ringer's (effect on the pulmonary and systemic microcirculations). Circ Shock 1983;10:179–88.
5. Fulton RL, Fischer RP. Pulmonary changes due to hemorrhagic shock resuscitation with isotonic and hypertonic saline. Surgery 1974;75:881–91.
6. Monafo WW, Halverson JD, Schechtman K. The role of concentrated sodium solutions in the resuscitation of patients with severe burns. Surgery 1984;95:129–35.
7. Monafo WW, Chuntrasakul C, Ayvazian VH. Hypertonic sodium solutions in the treatment of burn shock. Am J Surg 1973;126:778–83.
8. Caldwell FT, Bowser BH. Critical evaluation of hypertonic and hypotonic solutions to resuscitate severely burned children. Ann Surg 1979;189:546–52.
9. Moylan JA Jr, Reckler JM, Mason AD, Jr. Resuscitation with hypertonic lactate saline in thermal injury. Am J Surg 1973;125:580–4.
10. Demling RH, Selinger SL, Bland RD, et al. Effect of acute hemorrhagic shock on pulmonary microvascular fluid filtration and protein permeability in sheep. Surgery 1975;77:512–9.
11. Demling RH, Niehaus G, Will JA. Pulmonary microvascular response to hemorrhagic shock, resuscitation and recovery. J Appl Physiol 1979;46:498–503.
12. Halmagyi DFJ, Gillett DJ. Dogs versus sheep as hemorrhagic shock models. J Surg Res 1967;7:78–84.
13. McLaughlin RF, Tyler WS, Canada RO. A study of the subgross pulmonary anatomy in various mammals. Am J Anat 1961;108:149–58.
14. Lewis FR, Elings VB, Sturm JA. Bedside measurement of lung water. J Surg Res 1979;27:250–61.
15. Ruiz BC, Tucker WK, Kirby RR. A program for calculation of intrapulmonary shunts, blood-gas and acid–base values with a programmable calculator. Anesthesiology 1975;42:88–95.
16. Moss GS, Das Gupta TK, Newson B, et al. Effect of hemorrhagic shock on pulmonary interstitial sodium distribution in the primate lung. Ann Surg 1973;177:211–21.
17. Moss GS, Das Gupta TK, Newson B, et al. The effect of saline solution resuscitation on pulmonary sodium and water distribution. Surg Gynecol Obstet 1973;136:934–40.
18. Crandall ED, Staub NC, Goldberg HS, et al. Recent developments in pulmonary edema. Ann Intern Med 1983;99:808–22.
19. Rackow EC, Fein IA, Siegel J. The relationship of the colloid osmotic–pulmonary artery wedge pressure gradient to pulmonary edema and mortality in critically ill patients. Chest 1982;82:433–7.
20. DaLuz PL, Shubin H, Weil MH, et al. Pulmonary edema related to changes in colloid osmotic and pulmonary artery wedge pressure in patients after acute myocardial infarction. Circulation 1975;51:350–7.
21. Rackow EC, Fein IA, Leppo J. Colloid osmotic pressure as a prognostic indicator of pulmonary edema and mortality in the critically ill. Chest 1977;72:709–13.

22. Weil MH, Henning RJ, Morissette M, et al. Relationship between colloid osmotic pressure and pulmonary artery wedge pressure in patients with acute cardiorespiratory failure. Am J Med 1978;64:643–50.

23. Metildi LA, Shackford SR, Virgilio RW, et al. Crystalloid versus colloid in fluid resuscitation of patients with severe pulmonary insufficiency. Surg Gynecol Obstet 1984;158:207–12.

24. Moss GS, Siegel DC, Cochin A, et al. Effects of saline and colloid solutions on pulmonary function in hemorrhagic shock. Surg Gynecol Obstet 1971;133:53–8.

25. Rosenthal MH, Merrill DG, Mihm FG, et al. Reliability of COP and COP-PAW as indicators of lung water. Anesthesiology 1981;55:A81.

26. Gallagher TJ, Banner MJ, Barnes PA. Large volume crystalloid resuscitation does not increase extravascular lung water. Anesth Analg 1985;64:323–6.

27. Rackow EC, Falk JL, Fein IA, et al. Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. Crit Care Med 1983;11:839–50.

28. Gazitua S, Scott JB, Swindall B, Haddy FJ. Resistance responses to local changes in plasma osmolality in three vascular beds. Am J Physiol 1971;220:384–91.

29. Wildenthal K, Skelton CL, Coleman HN III. Cardiac muscle mechanics in hyperosmotic solutions. Am J Physiol 1969; 217:302–6.

30. Wildenthal K, Mierzwiak DS, Mitchell JH. Acute effects of increased serum osmolality on left ventricular performance. Am J Physiol 1969;216:898–904.

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1987;66:159–65

Fundamental Properties of Local Anesthetics

I. The Dependence of Lidocaine's Ionization and Octanol:Buffer Partitioning on Solvent and Temperature

Virgil Sanchez, MD, G. Richard Arthur, PhD, and Gary R. Strichartz, PhD

SANCHEZ V, ARTHUR GR, STRICHARTZ GR. Fundamental properties of local anesthetics. I. The dependence of lidocaine's ionization and octanol:buffer partitioning on solvent and temperature. Anesth Analg 1987;66:159–65.

The protonation equilibrium and hydrophobic character of lidocaine were characterized by its pK_a *and the octanol:buffer partition coefficients of the charged* (P^+) *and neutral* (P^0) *drug species. These measurements were accomplished by ultraviolet spectrophotometry of pure lidocaine HCl solutions at different temperatures, ionic strengths, and buffer concentrations. Corroboration of the* pK_a *determination by the potentiometric method and of the partition coefficients by gas chromatography validated the general application of the spectrophotometric technique. The* pK_a *increased with decreasing temperature (7.61 ± 0.06 at 36°C; 7.94 ± 0.04 at 26°C, in water; mean ± SD), increasing ionic strength (8.06 ± 0.02 at 26°C in 0.165 M NaCl) and increasing buffer capacity (8.28 ± 0.06 at 25°C in 0.15 M NaCl + 20 mM buffer). Octanol:buffer partition coefficients for both the protonated and the neutral species (expressed as mole fractions) increased upon warming: 0.55 ± 0.04 and 2666 ± 202, respectively, at 25°C, and 0.75 ± 0.09 and 3210 ± 272, respectively, at 36°C. Ionic strength and buffer concentration had no significant effect on either P value. The increase in* pK_a *at lower temperatures coupled with the decreased partition coefficients resulted in a nearly constant concentration of the protonated species in octanol as the system was cooled, whereas the concentration of the neutral species fell by more than 80%. This finding may explain the large increase in the impulse blocking potency of lidocaine observed upon nerve cooling, if the protonated anesthetic species is the more active form of the drug competing with the neutral species for a common binding site.*

Key Words: ANESTHETICS, LOCAL—physical properties.

Impulse blockade by local anesthetics is mediated by drug interactions at the plasma membrane. Experiments on perfused axons exposed to local anesthetics dissolved in extracellular or axoplasmic solutions (1) have demonstrated this membrane site of action, and revealed that the cationic species of drug applied from the cytoplasmic compartment is the more potent form. Furthermore, these studies suggest that for some aspects of impulse blockade ("use-dependent" block in particular), the binding of drug molecules to sodium channels themselves may be an essential step (2,3). The general observation that the more hydrophobic local anesthetics are more potent nerve blockers has been incorporated quantitatively in biophysical models of anesthetic action (4–6). "Hydrophobicities" were calculated in most of these experiments (as octanol:water partition coefficients) and the distribution of the neutral species of anesthetic alone was correlated with drug action (4,5,7). However, the high potency of both protonated amine local anesthetics (1,8) and their quaternary derivatives (2,9) requires a consideration of the concentration of cationic drug molecules in membranes. As a first step in our studies we have measured protonation equilibria and partition coefficients of local anesthetics in a system of aqueous and immiscible organic solvents.

Attempts have been made previously to simulate biomembranes using a simple solvent system, such as octanol or heptane, in water (4,10,11). Parameters such as distribution coefficients (Q), defined as the ratio at equilibrium of the concentration of total anesthetic in the organic phase ($[L_o]$) to the concentration of total anesthetic in the aqueous phase ($[L_a]$)

Supported by USPHS NIH Grant GM 15904 and funds from Astra Lakemedel, Ab, Södertalje, Sweden.

Received from the Anesthesia Research Laboratories, Brigham and Women's Hospital, and the Department of Pharmacology, Harvard Medical School, Boston, Massachusetts. Accepted for publication September 13, 1986.

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have been used to quantitate hydrophobicity (7,12). Factors not addressed by these studies are the interactions of the solvents used, utilization of conditions similar to those of physiologic experiments, and the use of different techniques to confirm the data produced. In the present study we have examined the influence of ionic strength, buffer capacity and temperature on local anesthetic distribution.

Furthermore, our results are expressed as partition coefficients (P_c), a more useful, selective measure than distribution coefficients. Defined as the ratio, at equilibrium, of the concentration of the individual species (neutral or charged) between the organic solvent and aqueous phase (P^0 or P^+, respectively), partition coefficients provide information on the hydrophobic nature of the separate species and their potential for interactions within various regions of bilayer membranes.

In this study we have three goals: 1) to establish a new method for deriving partition coefficients; 2) to offer plausible explanations for variations in previously measured and theoretically calculated partition values; and 3), by using lidocaine as our model local anesthetic, to define some factors that affect these partition values.

Materials and Methods

Determination of pK_a

A modification of the spectrophotometric method described by Albert and Serjeant (13) was used to measure the stoichiometric pK_a of lidocaine. A buffered aqueous solution saturated with octanol, containing 10 mM lidocaine, was adjusted to pH 4 or 11 using 1N HCl or 1N NaOH, respectively. The respective absorbances were then measured at 271.0 nm, and designated as A_I and A_N. A series of absorbances (A_S) measured at intermediate pH values were then used in the equivalent Henderson–Hasselbach equation for determination of the stoichiometric pK_a:

$$pH = pK_a + \log \frac{A_S - A_N}{A_I - A_S} \quad (1)$$

Using the same technique, pK_a determinations were performed in solutions of differing temperature, ionic strength, and buffering capacity.

The technique of Leeson and Brown was used to measure potentiometrically the pK_a of two solutions for comparison with spectrophotometrically determined values (14). This technique involves a nonlogarithmic analysis of the relationship between the amount of titrant added and its corresponding pH value.

Determination of Q Values

Distribution coefficients were determined using three different analytical techniques: spectrophotometric, gas chromatographic, and liquid scintillation spectrometry of radiolabelled anesthetic. Lidocaine (10 mM) was dissolved in standard aqueous medium (SAM, see Reagents and Solutions) at low pH, saturated with octanol, and the initial lidocaine concentration ($[\bar{L}]_{aq}$) was measured by one of the above three methods. An equal volume of octanol (previously equilibrated with SAM) was mixed with the aqueous solution for 5 min and the phases allowed to separate for 15 min. The pH of the aqueous phase was then measured. After the removal of 1-ml samples from each phase, the lidocaine concentration of only the aqueous phase ($[L]_{aq}$) was measured. The Q value was then calculated using the following equation:

$$Q = \frac{[\bar{L}]_{aq} - [L]_{aq}}{[L]_{aq}} \quad (2)$$

In several experiments the lidocaine concentration in the octanol phase was also measured directly by spectrophotometric and liquid scintillation methods and showed no difference from the quantity $[\bar{L}]_{aq} - [L]_{aq}$.

The aqueous octanol mixture was titrated progressively with 10N NaOH and Q values determined at different pH values. These data were subsequently used to calculate P^0 and P^+ (see Results for the method used). In one set of experiments the pH was reacidified from 6 to 4 with 6N HCl, with no difference between the initial and final Q values measured at the lower pH, indicating that irreversible changes in this parameter did not occur during the normal titration procedure. Distribution coefficients also were determined at two different temperatures, 26° and 36°C, and over a range of ionic strengths and buffering capacities.

Density Measurements

Densities (D) of both phases were determined gravimetrically. A stoppered 1-ml volumetric flask was dried and initially weighed on a Mettler balance (±0.00005 g). Separate 1-ml solutions of aqueous and organic phases, free of local anesthetics but equilibrated with each other, were then weighed at the relevant temperatures. Partition coefficients, expressed as the ratio of mole fractions (P_m), were cal-

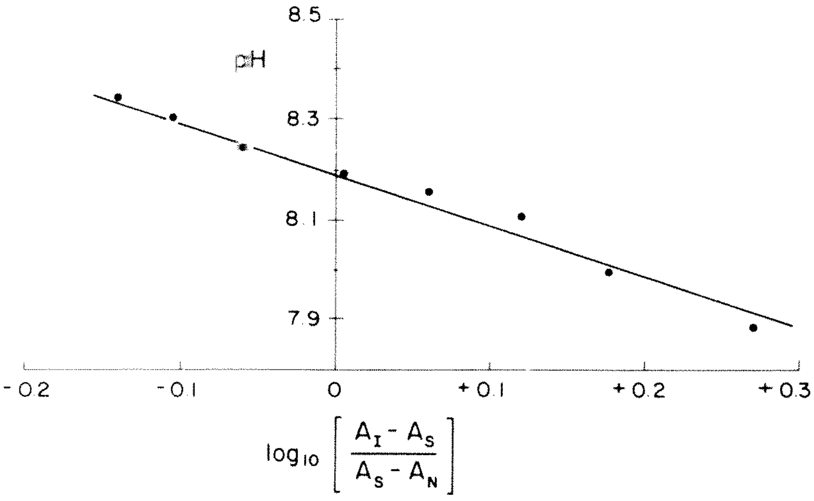

Figure 1. One typical spectrophotometric titration curve. Absorbance of a buffered solution of lidocaine, at 271 nm was measured at pH 4 to give A_I, the endpoint for the ionized form, and at pH 11 to give A_N, the endpoint of the neutral form. Absorbances at intermediate pH values, A_S, were subtracted from these endpoint values to yield the ratio of ionized to neutral drug, the $\log_{10}$ of which is here plotted as the abscissa. The straight line, fit to the points by linear least-squares regression analysis, intercepts the pH scale at the pK$_a$. The slope of the line, 1.04, indicates that a single proton is titrating this absorbance change. T = 25°C.

culated from the relative phase densities and the calculated values of partition coefficients expressed as concentrations (P_c):

$$P_m = P_c \times \frac{D_{aqueous}}{D_{octanol}} \times \frac{MW_{octanol}}{MW_{H_2O}} \qquad (3)$$

Reagents and Solutions

Reagents. Lidocaine HCl was a gift from Astra Pharmaceutical Corporation (Worcester, MA). ^{14}C-Labeled lidocaine (specific activity, 58.9 mC/mmol) was purchased from New England Nuclear Corporation (Boston, MA) and used within two months of synthesis. The 1-octanol (Fisher Certified 99.93% pure grade) was obtained from Fisher Scientific Company, Inc. (Fairlawn, NJ). The water was deionized using an ion-exchange system from Continental Deionized Water Service (Boston, MA).

Solutions. The standard aqueous medium (SAM) consisted of 150 mM NaCl, 5 mM MES (2-(N-morpholino)ethanesulfonic acid), 5 mM MOPS (morpholinopropane sulfonic acid), and 5 mM CAPS ((3-cyclohexylamino)-propane sulfonic acid) in water. Together these buffers provided a relatively constant buffering capacity from pH 5 to pH 11. Deionized water was saturated with octanol by mixing 25 ml of SAM and 1 ml of octanol for 10 min, then centrifuging the mixture at 900 × g for 20 min to separate the organic and aqueous phases. This procedure was performed at the same temperature at which experimental measures of pK$_a$ and Q were to be made. The octanol used for the determination of Q and pK$_a$ values was saturated with SAM using the same technique. The aqueous media used in the determination of pK$_a$'s were also saturated with octanol unless otherwise stated.

Analytic Techniques

pH Determination. The pH was measured by an Orion Research Model 701A Digital Ionilizer using an Ag/AgCl combination glass electrode (Cole-Parmer, Chicago, IL). The electrode was calibrated against reference solutions covering the narrowest pH range of interest, with drifts of measured pH being less than ±0.1 pH unit over a 1 hr period. All solutions were maintained at the desired temperature by a metal heating block (Reacti-Vap, Pierce Chemical Company, Rockford, IL).

Spectrophotometry. Absorbances of anesthetic solutions were measured with a Gilford Response UV-Vis Spectrophotometer (Gilford Instrument Laboratories, Inc., Overton, CA). Ultraviolet absorbance spectra of lidocaine HCl in SAM saturated with octanol, using matched quartz cuvettes, showed the following parameters: wavelength of maximum absorbance, 271.0 nm; ϵ(pH 4, 25°) = 0.273 cm^{-1}·mM^{-1}; ϵ(pH 11, 25°C) = 0.243 cm^{-1}·mM^{-1}. The molar absorptivity of lidocaine at 271 nm in octanol was the same as that in SAM at pH 11. Sealed solutions were incubated for a minimum period of 18 hr before spectrophotometric measurements of Q in order to ensure equilibrium and permit the escape of any microscopic bubbles.

Determinations of both pK$_a$ and Q values were performed using a double-walled, temperature controlled, 50-ml Reacti-Vial (Pierce Chemical Co., Rockford, IL) with an internal magnetic stirrer. Temperature

Table 1. pK_a of Lidocaine at Different Ionic Strength and Temperature

Solution	Temperature (°C)	Ionic strength (M)	pK_a	
			Spectrophotometric	Potentiometric
Water	26	0.05	7.94 ± 0.04^a ($n = 5$)	7.92 ± 0.03 ($n = 5$)
	36		7.55, 7.67^c	7.72, 7.56^c
165 mM NaCl	26	0.170	8.06 ± 0.02 ($n = 4$)	8.09 ± 0.02 ($n = 4$)
150 mM NaCl + 5 mM buffers[b]	26	~0.187	8.14 ± 0.04 ($n = 3$)	—
150 mM NaCl + 15 mM buffers (SAM)	25	~0.195	8.19 ± 0.03 ($n = 10$)	—
	36		7.77 ± 0.04 ($n = 10$)	—
150 mM NaCl + 20 mM buffers	25	~0.205	8.28 ± 0.06 ($n = 3$)	—

[a] Mean ± SD; the number of experiments is in parentheses.
[b] Buffers consist of 5 mM MES, 5 mM CAPS, and 5 mM MOPS.
[c] Both values where only two measurements were made.

was maintained using a water heating circulator (B. Brown Thermomix, Model 1420) and measured by a Model 42 SC Tele-Thermometer (Yellow Springs Instruments, Yellow Springs, OH).

Gas Chromatography. Gas chromatographic analysis was performed by means of a technique similar to that described by Tucker (15). Samples were diluted with distilled water to concentrations within the range of the assay (0.1–5.0 μg/ml). Measured concentrations of lidocaine HCl were between 1.00 and 3.00 μg/ml and the coefficient of variation of this assay in our laboratory is typically <5% at 1.0 μg/ml.

Liquid Scintillation. Aliquots of the organic and aqueous phases (0.1 ml each) were removed after equilibration and separation and added to 5 ml of scintillation cocktail (Aquasol 2, New England Nuclear, Boston, MA). Both solvents were miscible with this cocktail, which counted at about 80% efficiency (^{14}C) in a Beckman LS-6800 liquid scintillation counter.

Results

The ionization constant (pK_a) and octanol:buffer distribution coefficient (Q) for lidocaine were determined under a variety of conditions, and from these measured parameters the partition coefficients of charged and neutral species of the anesthetic were calculated.

Figure 1 is a typical titration curve showing the relationship between pH and the log of the ratio of absorbances of neutral and charged species of lidocaine. The data were well fit by a straight line; the stoichiometric pK_a, by definition, equals the pH at which the ratio of concentrations of neutral to charged species is unity. Using the same analysis, we determined lidocaine's pK_a in aqueous media at different ionic strengths and temperatures (see Table 1). An increase of temperature produced a significant decrease in pK_a, reflecting an increase in the effective proton dissociation constant, in agreement with the findings of Kamaya et al. (16). On the other hand, an increase in ionic strength increased the pK_a, and thereby elevated the concentration of the charged form at the expense of the neutral form. As the buffer concentration was raised, the pK_a also increased. The pK_a of lidocaine in octanol-saturated media did not differ from that in octanol-free media.

Comparison of these results with those obtained potentiometrically (Table 1) indicates no statistically significant difference between results from the two methods. This comparison confirms that spectrophotometric analysis can yield accurate and precise measures of pK_a, and spectrophotometric analysis has the added advantage of permitting the measurement of drug dissociation constants in buffered solutions.

The relationship between the measured octanol:buffer distribution coefficient (Q) and pH, as determined by the three analytical techniques used, is illustrated in Figure 2. Because the sensitivity of the spectrophotometric technique is limited by the aqueous concentration of the drug, which in turn depends on its solubility and pK_a, reliable Q measurements using spectrophotometry were confined to pH values below 6. Q values determined during back-titration with HCl showed no difference from values obtained during the initial titration with NaOH, demonstrating the chemical stability of the drug and the lack of effect of ions added during the titration.

Distribution of an ionizable compound between aqueous and organic phases reflects the extent of ionization and the relative partitioning of neutral and ionized species. The relationship between Q and pH can be mathematically derived:

$$Q = \frac{[L^0]_{org} + [L^+]_{org}}{[L^0]_{aq} + [L^+]_{aq}} \qquad (4)$$

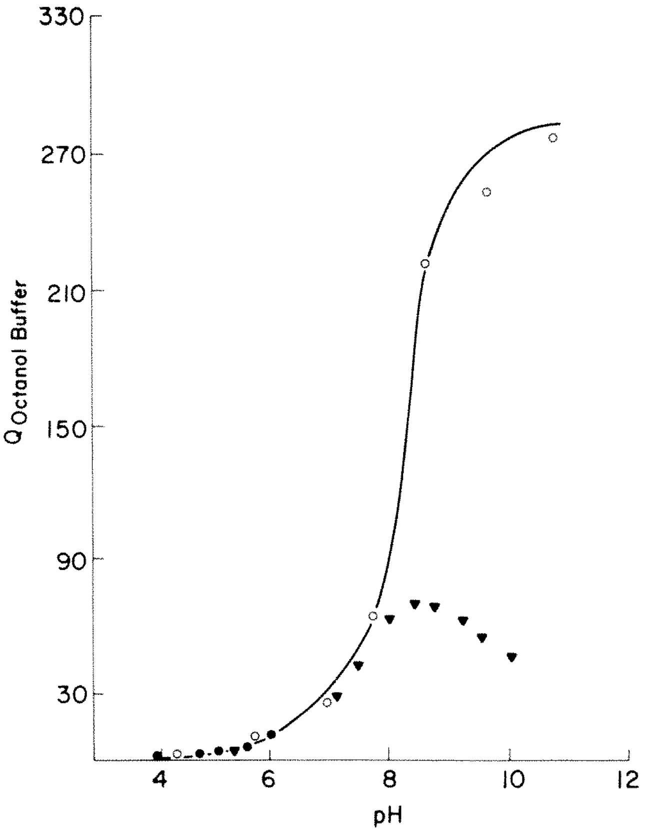

Figure 2. The ratio of lidocaine concentrations in octanol and buffer (SAM), Q, determined by spectrophotometry (●), gas chromatography (○), and liquid scintillation spectrometry of radiolabelled "lidocaine" (▼), over a range of pH values. T = 25°C. See the text for details of the methodology. The solid line is a graph of Equation 8 (see Results) with the β value determined from experiments like that in Figure 1 and the P_c values determined from fits to the linearized data, as shown in Figure 3.

where $[L^0]_{org}$ and $[L^0]_{aq}$ are the concentrations of the neutral species in the organic and aqueous phases, respectively, and $[L^+]_{org}$ and $[L^+]_{aq}$ are the corresponding concentrations of the charged species.

Because

$$P^0 = [L^0]_{org}/[L^0]_{aq} \quad \text{and} \quad P^+ = [L^+]_{org}/[L^+]_{aq}, \tag{5,6}$$

$$Q = \frac{P^0 + \dfrac{P^+[L^+]_{aq}}{[L^0]_{aq}}}{1 + \dfrac{[L^+]_{aq}}{[L^0]_{aq}}}. \tag{7}$$

Defining the aqueous ionization ratio, β, by $\beta = 10^{pK_a - pH} = [L^+]_{aq}/[L^0]_{aq}$ simplifies equation 7 to:

$$Q = \frac{P^0 + \beta P^+}{1 + \beta}. \tag{8}$$

Equation 8 describes Q as a function of three variables: β, P^0, and P^+. Once the pK_a has been determined, β can be calculated as a function of pH. A graph of $Q(1 + \beta)$ vs β should be linear; the slope and y intercept equal P^+ and P^0, respectively. Such an analysis, applied to the data of Figure 2, is illustrated in Figure 3. The predicted linear behavior of Equation 8 is evident, and it is thus possible to calculate P^0 and P^+ values by analyzing ΔQ over a narrow pH range. That these partition coefficients are constant over a much wider pH range is shown by the solid curve in Figure 2, a graph of Q calculated from Equation 8 and plotted against pH. Distribution coefficients measured by the more sensitive technique of gas chromatography agree well with the predicted behavior at 6 pH units higher than the measured spectrophotometric values (Fig. 2). In contrast, the results obtained by liquid scintillation of commercially available radiolabeled lidocaine (Fig. 2) do not agree with either of the other two measurements at pH values greater than 7.

The partition coefficients defined in Equations 5 and 6 and calculated by the method just described compare the concentrations of anesthetic (in mol/L) in two immiscible phases, a parameter we designate as P_c. Another mode of comparison instead relates the mole fraction (mole solute/total moles) of anesthetic in each phase, and is designated P_m. P_m was calculated from P_c values using Equation 3 (see Methods) along with the densities of the different phases measured at the relevant temperatures. The density measurements of the reciprocally equilibrated phases at different temperatures are (in g/ml): SAM (22°C) = 1.0021 ± 0.0008; SAM (37°C) = 0.9981 ± 0.0003; octanol (22°C) = 0.8264 ± 0.0003; octanol (37°C) = 0.8159 ± 0.0005. The two forms of the partition coefficients are listed in Table 2, which also reports the temperature dependence of these parameters. Raising the temperature from 25 to 36°C increases the partition coefficient of the neutral form by about 20% and that of the charged form by 50%.

Discussion

The procedures described in this article allow one to identify the important factors controlling distribution coefficients of local anesthetics. The variables of Equation 3, partitioning of individual species and the degree of ionization, are functions of temperature, ionic strength, and buffer behavior. Furthermore, the choice of organic solvent greatly influences the overall distribution of lidocaine between the two phases. Unfortunately, most values presented in the existing literature do not define these conditions, and others are derived from theoretical considerations alone.

The octanol:buffer distribution coefficient may be

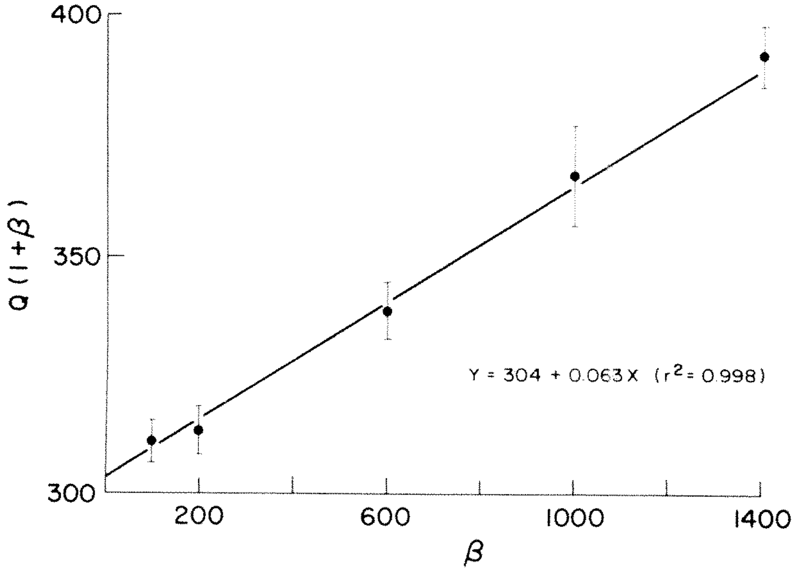

Figure 3. A graph of the linearized distribution data, as defined by equation 8. Spectrophotometric determinations of the distribution coefficient (Q) were made at each pH (means ± SEM shown by the error bars; $n = 3$) and plotted against the ionization ratio, β, calculated from the pH measured in this experiment and the average pK_a from five independent separate titrations. The pH ranged from 4 to 6, T = 25°C, and the buffer was SAM. The straight line, fit to the unweighted means by linear least-squares regression, has a y-axis intercept of 304 ($= P_c^0$) and a slope of 0.063 ($= P_c^+$), with a correlation coefficient closely approaching unity.

more physiologically pertinent than octanol:water values because buffers are reactants in the normal ionization of local anesthetics. The actual distribution of drugs into membranes in vivo occurs from strongly buffered solutions of 0.1–0.2 M ionic strength. Measured in a similarly defined aqueous environment, the distribution coefficients include the effect of temperature and ionic strength on the buffers as well as on the local anesthetic alone. In the present experiments we chose a series of "Good" zwitterionic buffers (17) with pK_a values that provided a relatively constant buffering capacity throughout the pH range used, and that have minimum temperature dependences. The normal endogenous buffers (e.g., bicarbonate-CO_2, ATP, proteins, and lipids) will have different temperature and ionic strength dependences than those of "Good" buffers, and thus, different effects on the overall ionization of the anesthetic molecules in different aqueous and membranous compartments of the cell.

It is worthwhile to note here the difference between the true "thermodynamic" proton dissociation constant of local anesthetics and the "stoichiometric" value reported here. Our measurement represents the ratio of concentrations of ionized and free base forms, whereas the thermodynamic value explicitly involves the activity coefficients of these species (13). The expected differences between the two pK_a's will be small for solutions of low ionic strength (<0.01 M), but will grow with increasing ionic strength in a manner dependent on the radius of the protonated molecule, as described by the expanded Debye–Huckel theory (18). We will address this phenomenon in a subsequent paper.

According to the tabulations of Hansch and Leo (19,20), the partition coefficient of neutral lidocaine (P^0) in an octanol/water system is 190, considerably lower than the value of 300 reported here for 25°C. However, Broughton et al. (7) reported a P^0 value of 268 using HPLC, in agreement with our result, and with the value of 280 reported in the original description by Löfgren (21).

In this study, the distribution coefficients obtained by liquid scintillation spectrometry of ^{14}C-labeled lidocaine were significantly different from those found by other methods. The dependence of Q on pH also departed from the theoretically predicted behavior, as Q values actually decreased at pH values greater than pH 8.5 (Figure 1). However, Ueda et al. reported very similar values derived by the same technique (10,22). We believe these results to be artifactual for the following two reasons: 1) the results cannot be duplicated by other methods; and 2) the behavior of Q vs pH is not thermodynamically consistent. Thus, the anomalous behavior may be due to radioactive impurities. Minor impurities may have major consequences, depending on their partitioning behavior compared to the drug under investigation. For example, substitution into Equation 7 shows that a 1% impurity (of a nonionizable substance) having a partition coefficient of $P_I = 0.1$ will reduce the distribution coefficient at the pK_a by almost threefold.

Although the distribution coefficient represents the overall uptake of drug, the partition coefficient determines the contribution made by each species. As the temperature is decreased from 37°C to 26°C, the distribution coefficient as well as the partition coefficient of the neutral form decreases slightly, whereas

Table 2. Temperature Dependence of Octanol:Buffer Partition Coefficients of Lidocaine

	P^+		P^0	
Temperature (°C)	P_c	P_m	P_c	P_m
25 (n = 3)	0.063 ± 0.005	0.55 ± 0.04	304 ± 23	2666 ± 202
36 (n = 3)	0.085 ± 0.010	0.75 ± 0.09	366 ± 31	3210 ± 272

Abbreviations: P^+, octanol:buffer partition coefficient of charged drug species; P^0, octanol:buffer partition coefficient of neutral drug species; P_c, partition coefficient as ratio of concentration (moles solute/liter solution); P_m, partition coefficient as ratio of mole fraction (moles solute/total moles).

the partition coefficient of the charged species, P^+, falls by a third (Table 2). The pK_a of lidocaine in this buffer system rises with the fall in temperature (Table 1). The net effect of cooling, contributed to by changes in both ionization and partitioning, is to decrease the concentration of the charged species in the hydrophobic phase by 10% while reducing that of the neutral species by 60%. Direct measurement of the lidocaine content of mammalian sciatic nerve shows a reduction in total anesthetic uptake with decreasing temperature (a 45% decrease from 37 to 20°C), although the effect of lidocaine in blocking nerve impulses, both in vitro and in vivo, is potentiated by cooling (12,23,24). Such correspondences are consistent with the relatively greater affinity of the protonated species of 3°-amine anesthetics over that of the competing neutral species for a common site of action on the neuronal sodium channel (8,25,26).

We thank Ms. Shilpa Shah for technical assistance with gas chromatography and Ms. Bonnie Brugger for typing the manuscript. Dr. Sanchez is a Fellow for the Harvard Center for Research and Training in Anaesthesia.

References

1. Narahashi T, Frazier D, Yamada M. The site of action and active form of local anesthetics. I. Theory and pH experiments with tertiary compounds. J Pharm Exp Ther 1970;171:32–44.
2. Strichartz GR. The inhibition of sodium currents in myelinated nerve by quaternary derivatives of lidocaine. J Gen Physiol 1973;62:37–57.
3. Courtney KR. Mechanism of frequency-dependent inhibition of sodium currents in frog myelinated nerve by the lidocaine derivative GEA-968. J Pharm Exp Ther 1975;195:225–36.
4. Courtney K. Structure-activity relations for frequency-dependent sodium channel block by local anesthetics. J Pharm Exp Ther 1980;213:114–9.
5. Courtney KR, Etter EF. Modulated anticonvulsant block of sodium channels in nerve and muscle. Europ J Pharmacol 1983;88:1–9.
6. Bradley DJ, Richards CD. Temperature-dependence of the action of nerve blocking agents and its relationship to membrane-buffer partition coefficients. Thermodynamic implications for the site of action of local anesthetics. Br J Pharmacol 1984;81:161–7.
7. Broughton A, Grant A, Starmer F, Klinger J, Stambler B, Strauss H. Lipid solubility modulation pH potentiation of local anesthetic block of V_{max} reactivation on guinea pig myocardium. Circ Res 1984;55:513–23.
8. Schwarz W, Palade PT, Hille B. Local anesthetics: effect of pH on use-dependent block of sodium channels in frog muscle. Biophys J 1977;20:343–68.
9. Frazier DT, Narahashi T, Yamada M. The site of action and active form of local anesthetics. II. Experiments with quaternary compounds. J Pharmacol Exp Ther 1970;171:45–51.
10. Ueda I, Oguchi K, Arakawa K. True octanol/water partition coefficients of procaine and lidocaine and estimation of their dissociation constants in organic solvents. Anesth Analg 1982;61:56–61.
11. Kaufman JJ, Semo N, Koski W. Microelectrometric titration measurement of the pK_a's and partition and drug distribution coefficients of narcotics and narcotic antagonists and their pH and temperature dependence. J Med Chem 1975;18:647–55.
12. Rosenberg PH, Heavner JE. Temperature-dependent nerve-blocking action of lidocaine and halothane. Acta Anaesth Scand 1980;24:314–20.
13. Albert A, Serjeant EP. Ionization constants of acids and bases. London: Methuen & Co., Ltd., 1962:69–92.
14. Leeson LJ, Brown M. Some observations on nonlogarithmic titration curves for the determination of dissociation constants and purity. J Pharm Sci 1966;55:431–3.
15. Tucker GT. Determination of bupivacaine (Marcaine) and other anilide type local anesthetics in human blood and plasma by gas chromatography. Anesthesiology 1970;32:255–60.
16. Kamaya H, Hayes JJ, Ueda I. Dissociation constants of local anesthetics and their temperature dependence. Anesth Analg 1983;62:1025–30.
17. Good N, Winget GD, Winter W, Connolly T, Izawa S, Singh RMM. Hydrogen ion buffers for biological research. Biochemistry 1966;5:467–77.
18. Levy RH, Rowland M. Determination of thermodynamic dissociation constants of local anaesthetic amines: influence of ionic strength. J Pharm Pharmacol 1972;24:841–7.
19. Hansch C, Leo A. Subsequent constants for correlation analysis on chemistry and biology. New York: John Wiley & Sons, 1979.
20. McKenzie WL, Foge WD. Local anesthetic activity of 2-piperazine-carboxanilides. J Med Chem 1972;15:291.
21. Löfgren N. Studies on local anesthetics. Xylocaine: a new synthetic drug. Stockholm, Sweden: Ivar Haeggstioms, 1948.
22. Ueda I, Yasuhara H, Shieh DD, Lin H-C, Lin SH, Eyring H. Physical chemistry of the interaction of local anesthetics with model and natural membranes. Prog Anesth 1980;2:285–94.
23. Bokesh P, Strichartz G. Temperature modulation of use-dependent local anesthetic block. Reg Anesth 1983;8:49.
24. Strichartz G, Zimmermann M. Selective conduction blockade among different fiber types in mammalian nerves by lidocaine combined with low temperature. Soc for Neuroscience (USA), Abstracts 1983;9:675.
25. Hille B. The pH-dependent rate of action of local anesthetics on the node of Ranvier. J Gen Physiol 1977;69:475–96.
26. Schmidtmayer J, Ulbricht W. Interaction of lidocaine and benzocaine in blocking sodium channels. Pflugers Arch 1980; 387:47–54.

ANESTH ANALG
1987;66:166–70

Narcotics Decrease Heart Rate during Inhalational Anesthesia

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CAHALAN MK, LURZ FW, EGER EI II, SCHWARTZ LA, BEAUPRE PN, SMITH JS. Narcotics decrease heart rate during inhalalational anesthesia. Anesth Analg 1987;66:166–70.

We determined the heart rate (HR) response to enflurane, halothane, and isoflurane and the effects of narcotics on this response in 81 healthy patients scheduled for elective surgery. Patients were randomly assigned to one of six treatment groups: one of the three anesthetics (approximately 0.9 MAC) in 60% nitrous oxide, and either 0.15 mg/kg of intramuscular morphine 30–60 min before induction or 1 μg/kg of IV fentanyl 10 min after skin incision. All patients received diazepam, 10 mg orally, 60–90 min before anesthesia, a rapid sequence intravenous induction, and mechanically controlled ventilation. During inhalational anesthesia and the first 10 min of surgery, no significant change in HR occurred in any group (compared to the preinduction HR), although patients given morphine premedication tended to have a decreased HR and those not given morphine premedication tended to have an increased HR. These trends partially account for significant differences that emerged between groups after induction of anesthesia. Patients given morphine premedication and halothane had lower HR (64 ± 3 SEM) than patients given isoflurane (80 ± 3) or enflurane (84 ± 3) and no morphine premedication. Patients anesthetized with enflurane and morphine premedication had lower HR (71 ± 3) than patients given enflurane without morphine premedication. Administration of fentanyl 10 min after incision (these patients had received no morphine) significantly decreased HR in the presence of any of the vapors. We conclude that inhalational anesthetics used in the clinical setting we employed do not significantly increase heart rate, and that prior administration of morphine or concurrent administration of fentanyl may significantly decrease HR.

Key Words: ANESTHETICS, VOLATILE—enflurane, halothane, isoflurane. ANALGESICS—fentanyl, morphine. HEART—pulse rate.

In young healthy volunteers not subjected to surgery, enflurane (1) and isoflurane (2) increase heart rate (HR) 20–40%, whereas halothane does not increase HR (3). All three anesthetics decrease mean arterial pressure by 30–50% (1–3). Because increased HR and low blood pressure can cause myocardial ischemia, not all surgical patients will tolerate the hemodynamic alterations reported for enflurane and isoflurane. However, we have observed smaller increases in HR in adult surgical patients anesthetized with enflurane or isoflurane at our medical center than were reported to occur in volunteers. In addition, we have observed decreases in HR when a narcotic agent is used preoperatively or intraoperatively during anesthesia with any of the three anesthetics. To test these clinical observations, we compared the effects of the three anesthetics on HR, and determined whether premedication, including morphine or intraoperative administration of fentanyl, altered either HR or blood pressure response to these agents.

Methods

After approval by our Committee on Human Research, and informed consent from patients, we studied 81 healthy (physical status ASA I or II) adults scheduled for elective surgery. We selected patients who would remain in the supine or lithotomy position for surgery, excluding any patient requiring a procedure involving the brain, chest cavity, or aorta. We also excluded patients chronically treated with narcotics, β-blockers, or anticholinergic agents.

All patients were given oral diazepam, 10 mg 60–90 min before induction of anesthesia. Initially, each patient was assigned by means of a random number table to one of nine treatment groups: 1) one of the

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Support for this work was supplied in part by the Anesthesia Research Foundation, and the National Institutes of Health, 1R23GM28502-03 (MKC) and AG 03104 (EIE).

Received from the Department of Anesthesia, University of California Medical Center, San Francisco, California. Accepted for publication August 4, 1986.

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Table 1. Summary of Preanesthetic Data

Group	n	Age (yr)	Weight (kg)	ASA physical status	WardHR (beats/min)	WardMAP (mm Hg)	Preinduction HR (beats/min)	Preinduction MAP (mm Hg)
HAL F	9	39 ± 3	67 ± 3	1.3	75 ± 3	82 ± 3	78 ± 4	90 ± 3
ENF F	12	45 ± 4	65 ± 4	1.3	81 ± 3	94 ± 3	80 ± 5	97 ± 3
ISO F	17	39 ± 4	68 ± 4	1.3	77 ± 3	89 ± 3	77 ± 3	94 ± 4
HAL MS	14	39 ± 3	65 ± 3	1.1	77 ± 3	91 ± 4	70 ± 4	92 ± 3
ENF MS	15	41 ± 4	65 ± 5	1.1	79 ± 2	89 ± 2	80 ± 4	94 ± 2
ISO MS	14	42 ± 3	69 ± 4	1.3	80 ± 3	87 ± 3	78 ± 4	97 ± 4

Values are given as the mean ± SEM.

Abbreviations: HR, heart rate; MAP, mean arterial pressure; HAL, halothane; ENF, enflurane; ISO, isoflurane; F, groups given fentanyl, 1.0 μg/kg IV, 10 min after skin incision; MS, groups given morphine sulfate, 0.1 mg/kg intramuscularly, 30–60 min before induction of anesthesia.

three inhalational anesthetics and morphine, 0.15 mg/kg intramuscularly, 30–60 min before induction of anesthesia; 2) one of the three anesthetics and morphine, 0.1 mg/kg IV, 10 min after skin incision; or 3) one of the three anesthetics and fentanyl, 1.0 μg/kg IV, 10 min after skin incision. We selected 0.15 mg/kg of morphine for premedication and 1 μg/kg of fentanyl intraoperatively because we commonly use these doses in our practice. The intraoperative dose of morphine (0.1 mg/kg) was selected as the approximate equivalent of the fentanyl dose. We selected 10 min after incision as the moment for administration of the intraoperative narcotic because we assumed this would be a period of fairly stable surgical stimulation.

Prior to anesthesia, electrocardiographic (ECG) monitoring was established in each patient, and any fluid deficit secondary to fasting was replaced with lactated Ringer's solution (0.5 ml·kg^{-1}·hr^{-1} of fasting) administered through a large bore catheter. The infusion rate was maintained at 5 ml·kg^{-1}·hr^{-1}, unless the anesthesiologist decided that the patient required additional fluid. In all cases, the amount of fluid administered was recorded. An automated blood pressure and heart rate monitor (Dinamap® model 845 by Critikon, Tampa, FL) was placed on the arm without the catheter and set to cycle and record (Dinamap® model 950) each minute for the duration of the study.

Once three successive readings of HR and mean arterial pressure (MAP) varied less than 10%, 100% oxygen was delivered by face mask and 3 mg of *d*-tubocurarine were injected intravenously. Three minutes later, each patient was given thiopental, 4 mg/kg, and succinylcholine, 1.5 mg/kg. Immediately after the onset of muscle relaxation, the trachea was intubated. Ventilation was then controlled to maintain end-tidal CO_2 between 28–32 mm Hg. Inspired concentrations of inhalation anesthetic were sufficient to achieve (within 5 min of intubation) and maintain an end-tidal concentration of 60% N_2O and the predetermined concentration of vapor: 0.7% halothane, 1.5% enflurane, or 1.0% isoflurane. All concentrations of the vapors and gases were measured by mass spectrometry.

When one of the first two patients given 0.1 mg/kg morphine intraoperatively became hypotensive (MAP < 50 mm Hg), we interrupted the study. Because the hypotensive effects of morphine are dose-dependent, we halved the intraoperative dose. Despite this reduction, two of the next eight patients given the reduced dose became hypotensive. Although none developed perioperative complications related to hypotension, we decided to eliminate from the study the three groups given morphine intravenously. Thus only six treatment groups remained: those given one of the three vapors and morphine, 0.15 mg/kg intramuscularly, 30–60 min before induction; and those given one of the vapors and fentanyl, 1.0 μg/kg IV, 10 min after incision.

Heart rate and mean arterial pressure were analyzed at seven intervals during the study: 1) ward, the means of the first measurements taken on admission and the last taken before leaving the ward for the operating room; 2) preinduction, the means of the three measurements taken immediately before administration of *d*-tubocurarine; 3) postinduction, the means of values obtained at 14 and 15 min after intubation and before incision; 4) postincision 5, the means of values obtained at 4 and 5 min after incision; 5) postincision 10; 6) postincision 15; and 7) postincision 20 (the last three are the means of values obtained at the defined times). The study terminated with postincision 20 measurements. Because the HR and MAP were recorded each minute, we identified the minimum and maximum value of these variables in each of the intervals. Except during the few minutes before and after intubation (when the inhalational anesthetics were either absent or at minimal concentrations), the minimum and maximum values were usually the same as the values obtained at the moments defined above. Therefore, we present only the data

Table 2. Summary of Intraoperative Treatments and Values

Group	n	Anesthetic depth (%)	CO_2 (mm Hg)	Fluid administration (ml)	Temperature (°C)
HAL F	9	0.70 ± 0.01	32 ± 1	686 ± 51	36.1 ± 0.1
ENF F	12	1.51 ± 0.02	32 ± 1	817 ± 32	35.5 ± 0.2
ISO F	17	1.00 ± 0.02	30 ± 1	836 ± 48	35.5 ± 0.3
HAL MS	14	0.72 ± 0.01	30 ± 1	677 ± 52	35.7 ± 0.2
ENF MS	15	1.52 ± 0.02	32 ± 1	772 ± 61	36.3 ± 0.2
ISO MS	14	1.00 ± 0.02	29 ± 1	969 ± 138	35.9 ± 0.2

Values are mean ± SEM.

Abbreviations: HAL, halothane; ENF, enflurane; ISO, isoflurane; F, groups given fentanyl, 1.0 μg/kg IV, 10 min after skin incision; MS, groups given 0.1 mg/kg intramuscularly, 30–60 min before induction of anesthesia.

obtained at the times specifically given above. Temperature was monitored in all patients and no other drugs given except antibiotics or succinylcholine. 20 mg bolus, (always given 4 min before any measurement interval and only at the request for additional relaxation).

Within each group, changes in HR and MAP during the study were assessed by repeated measures analysis of variance. When this analysis indicated a significant change, multiple unpaired t-tests were used to identify the interval(s) where HR or MAP had changed from preinduction values. Between groups at each interval, data were compared by analysis of variance, and when this analysis indicated a significant difference, multiple t-tests were used to identify the differing groups. In the fentanyl groups, patients received no narcotic until 10 min after the start of surgery. Thus, data gathered from these patients before fentanyl administration indicate the response to induction of anesthesia and the start of surgery in the absence of any narcotic. For all statistical tests, a P-value of less than 0.05 was assumed to indicate significance, except where adjusted by the Bonferroni correction for multiple comparisons. Values in the text and figures are given as the mean ± SEM.

Results

Patients in the six groups were comparable in age, weight, ASA status, and ward and preinduction HR and MAP (Table 1). Immediately before induction, the three groups premedicated with diazepam alone had HR and MAP readings comparable to those in the groups premedicated with both diazepam and morphine (Table 1). Intraoperative management of fluid administration, anesthetic depth, temperature, and ventilation were also comparable (Table 2).

Induction of anesthesia and the first 10 min of surgery did not significantly alter HR in individual groups (Figs. 1 and 2). In the next (final) 10 min of the study, HR decreased significantly in the patients given intravenous fentanyl (Fig. 2) but did not change in the patients in the other three groups (Fig. 1).

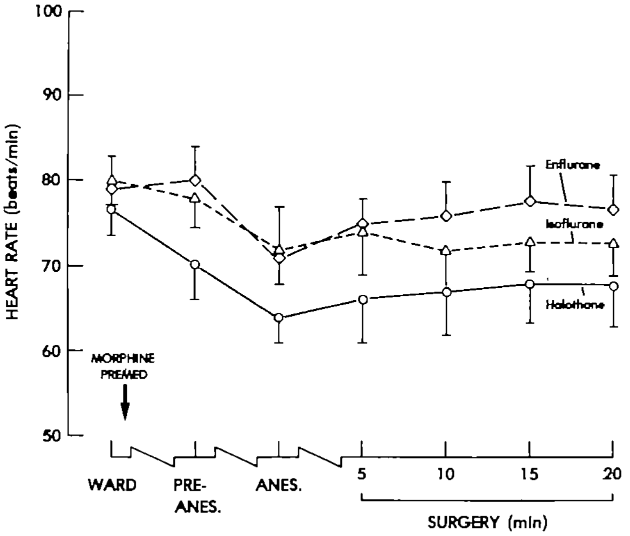

Figure 1. The mean and SEM of HR in each study group are plotted for each interval. All patients in the three groups were premedicated with both oral diazepam and IM morphine. No statistically significant changes in HR occurred.

Comparisons of HR among groups at each interval revealed three significant differences, all at the postinduction interval. After premedication with morphine, halothane anesthesia lowered HR (64 ± 3) relative to isoflurane (80 ± 3) or enflurane (84 ± 3) anesthesia without narcotic premedication. Heart rate in patients given enflurane and premedicated with morphine was also lower (71 ± 3) than HR in patients given enflurane without narcotic premedication (84 ± 3).

After induction, all six anesthetic combinations decreased MAP (Figs. 3 and 4). MAP increased slightly with surgery. Intravenous administration of fentanyl decreased MAP in patients anesthetized with halothane or isoflurane (Fig. 4). Patients given morphine

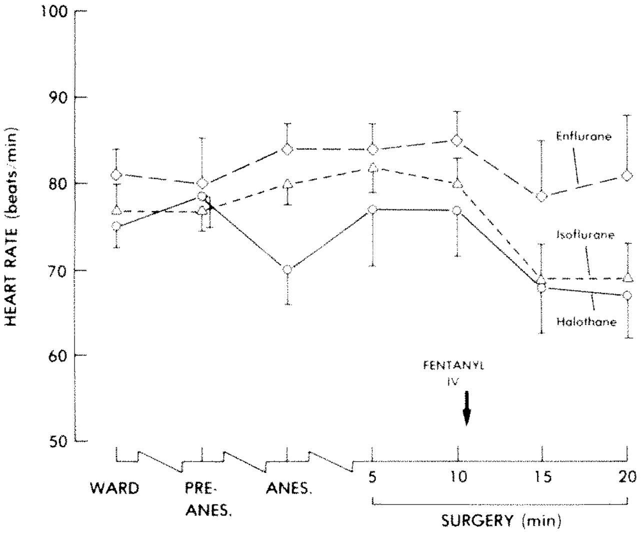

Figure 2. The mean and SEM of HR in each study group are plotted for each interval. All patients in the three groups were premedicated with oral diazepam (no narcotic) and were given IV fentanyl after 10 min of surgery. Statistically significant changes in HR followed administration of IV fentanyl with all three inhalational anesthetics.

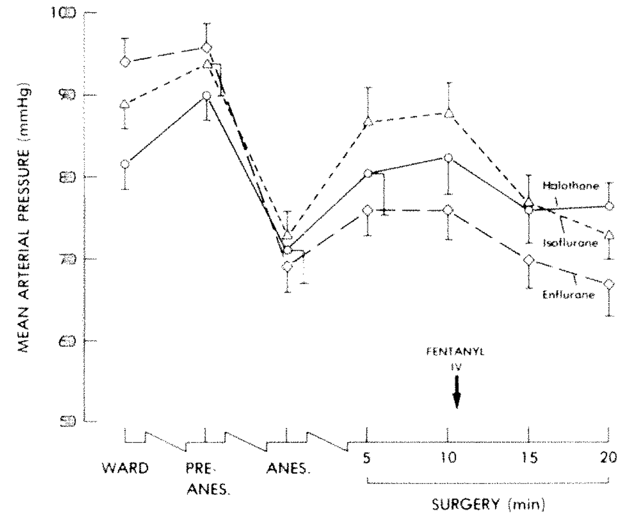

Figure 4. The mean and SEM of MAP in each study group are plotted for each interval. All patients in the three groups were premedicated with oral diazepam (no morphine) and given IV fentanyl after 10 min of surgery. Induction of anesthesia resulted in a significant decrease in MAP in all treatment groups. Administration of IV fentanyl significantly decreased MAP in patients anesthetized with halothane and isoflurane.

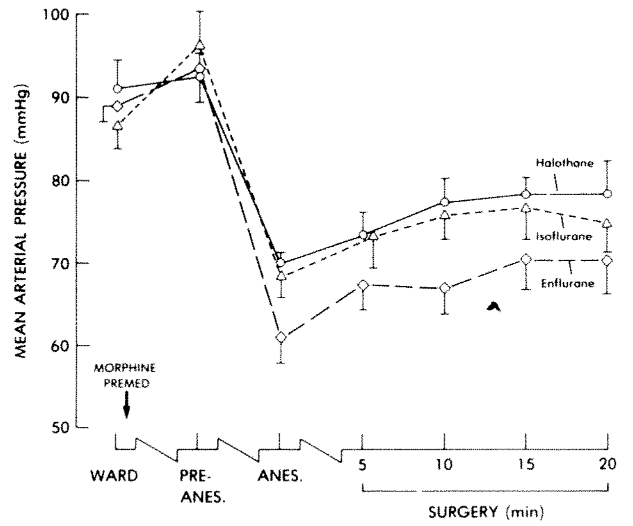

Figure 3. The mean and SEM of the MAP in each study group are plotted for each interval. All patients in the three groups were premedicated with oral diazepam and IM morphine. Statistically significant decreases in MAP occurred after induction with all three inhalational anesthetics.

preoperatively did not receive fentanyl and demonstrated no significant change in MAP after the onset of surgery (Fig. 3).

Comparisons of MAP of all groups at each interval revealed significant differences at two intervals. At both 5 and 10 min after incision, MAP in patients premedicated with morphine and anesthetized with enflurane was lower than MAP in patients given isoflurane after premedication with diazepam alone (67 ± 3 and 67 ± 3 vs 87 ± 4 and 88 ± 4).

Discussion

In contrast with results in volunteers, our patients given 0.9 MAC enflurane and isoflurane after diazepam premedication and induction with thiopental had no increase in HR. Several factors may explain this difference. First, our patients were two decades older than the volunteers. The multicenter clinical evaluation of isoflurane documents decreasing pulse lability with increasing age; after induction of anesthesia, HR increases averaged 2.2 beats/min in patients younger than 40 years of age but less than 1.0 beats/min in patients over the age of 40 (4). Second, our patients had higher preinduction HR than did the volunteers. The multicenter study found that heart rate changes associated with anesthesia were inversely related to the heart rate previous to anesthesia. A third and apparent difference is that our patients were given anesthetic adjuvants including diazepam, thiopental, and nitrous oxide in all cases. We specifically avoided factors which might have produced tachycardia, such as hypercarbia, hypovolemia, the administration of pancuronium, or inadequate anesthesia.

Our hypothesis that the intraoperative use of fentanyl decreases HR during inhalational anesthesia was confirmed by our within-group analysis (repeated measures analysis of variance); 1 μg/kg intravenous fentanyl significantly decreased HR regardless of the inhalational anesthetic used. The effects of premedication with morphine on HR are more difficult to interpret. No significant change in HR occurred in any of the groups given morphine. However, for patients who received enflurane and isoflurane, the tendency to increase HR without morphine premedication but decrease HR with morphine premedication (compare Fig. 1 to Fig. 2) suggests that morphine premedication decreases HR during anesthesia and surgery. Our between-groups analysis (analysis of variance) provides further evidence for the validity of this suggestion; at the postinduction interval in patients receiving enflurane, HR was lower if premedication included morphine than when premedication was with diazepam alone. Heart rate tended to decrease when halothane was given with or without premedication with morphine. We found a significant difference in HR between inhalational anesthetic groups only when morphine and halothane were combined. At the postinduction interval, patients who received halothane after premedication with morphine had a lower HR than patients who received isoflurane or enflurane after premedication with diazepam alone.

Therefore, in agreement with the multicenter evaluation of isoflurane, we found that the preoperative use of morphine or intraoperative use of fentanyl decreased HR during inhalational anesthesia. We did not investigate the mechanism producing the decrease in HR, but it is likely to be the direct vagotonic effects of morphine (5) and fentanyl (6). Although the addition of narcotics deepened the level of anesthesia, anesthetic depth alone is not a likely explanation for slower HR. Studies of isoflurane and enflurane in volunteers have previously documented that an increase in the concentration of these vapors either increases or does not change HR (1,2).

Patients in our study who received morphine premedication generally had a lower MAP after induction of anesthesia and throughout the first 10 min of surgery than patients who had premedication with diazepam alone. However, they also generally had a lower HR during these periods. Similarly, in patients who received fentanyl, both MAP and HR usually decreased. But, because decreases in HR and MAP both lower myocardial oxygen demand, our results suggest that the balance of myocardial oxygen supply and demand may have been favorably influenced by the narcotics. Thus when modest increases in HR may place a patient at risk, premedication including morphine may be advantageous if inhalation anesthetics are to be used; and, when intraoperative increases in HR place a patient at risk, administration of a small dose of fentanyl may be an effective therapy.

The authors wish to thank Celeste Mangold for help in the preparation of this manuscript and Winifred von Ehrenburg for editorial advice.

References

1. Calverley RK, Smith NT, Prys-Roberts C, Eger EI II, Jones CW. Cardiovascular effects of enflurane anesthesia during controlled ventilation in man. Anesth Analg 1978;57:619–28.
2. Stephens WC, Cromwell TH, Halsey MJ, Eger EI II, Shakespeare TF, Bahlman SH. The cardiovascular effects of a new inhalational anesthetic, Forane®, in human volunteers at constant arterial carbon dioxide tension. Anesthesiology 1971;35:8–16.
3. Eger EI, II, Smith NT, Stoelting RK, Cullen DJ, Kadis LB, Whitcher CE. Cardiovascular effects of halothane in man. Anesthesiology 1970;32:396–409.
4. Forrest JB. Clinical evaluation of isoflurane: pulse and blood pressure. Can Anaesth Soc J 1982;29:S15–S27.
5. Robbins BH, Fitzhugh OG, Baxter JH, Jr. The action of morphine in slowing the pulse. J Pharmacol Exp Ther 1939;66:216–23.
6. Liu WS, Bidwai AV, Stanley TH, Isern-Amaral J. Cardiovascular dynamics after large doses of fentanyl and fentanyl plus nitrous oxide in the dog. Anesth Analg 1976;55:168–72.

ANESTH ANALG 171
1987;66:171–6

Plain or Hyperbaric Bupivacaine for Spinal Anesthesia

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STIENSTRA R, VAN POORTEN JF. Plain or hyperbaric bupivacaine for spinal anesthesia. Anesth Analg 1987;66:171–6.

Three ml of bupivacaine 0.5%, either plain or in 8% glucose, was injected intrathecally in three groups of twenty patients. Group 1 received bupivacaine 0.5% plain; group 2 received bupivacaine 0.5% in 8% glucose. Patients in groups 1 and 2 were kept sitting for 3 min after injection. Patients in group 3 received bupivacaine 0.5% in 8% glucose and were placed in the supine horizontal position immediately after injection. Observations of patients in group 3 were observer blind and in groups 1 and 2 double blind. The differences between segmental levels of sensory and temperature loss between groups 1 and 2 and between groups 2 and 3 were statistically not significant. Motor blockade of the lower extremities was more intense in the patients who were kept sitting for 3 min (groups 1 and 2). It is concluded that both solutions are equally suitable for spinal anesthesia, provided patients receiving the plain solution are kept sitting for at least 2 min. When using hyperbaric bupivacaine, posture seems to have no influence on cephalad spread.

Key Words: ANESTHETIC TECHNIQUES—spinal. ANESTHETICS, LOCAL—bupivacaine.

In recent years, bupivacaine 0.5% has been used increasingly for spinal anesthesia, both as a plain and as a hyperbaric solution. The hyperbaric solution of bupivacaine has been found to be a safe and reliable anesthetic solution for spinal anesthesia in various studies (1–4). The plain solution of bupivacaine 0.5% has also been used for spinal anesthesia with good results (5–11). Others, however, found the plain solution of bupivacaine unsatisfactory or only suitable for perineal and lower limb surgery (3,12–16). Since 1982 our department has used the plain solution of bupivacaine 0.5% as the sole agent for spinal anesthesia. We have accumulated experience in over 3000 cases in which the plain solution proved an excellent spinal agent for any kind of surgery below the umbilicus. Because of conflicting findings in the literature with regard to the effectiveness of the plain solution, the present study was undertaken to compare the effects of hyperbaric bupivacaine with those of plain bupivacaine under double blind conditions, and the effect of posture when using the hyperbaric solution under observer-blind conditions.

Patients and Methods

Sixty patients (ASA I–II) about to undergo urologic surgery under spinal anesthesia were randomly allocated to either a double-blind group (groups 1 and 2) or the open group (group 3). Each group contained twenty patients. Patients in the double-blind groups received 3 ml of a solution containing either bupivacaine 0.5% plain (group 1) or bupivacaine 0.5% in glucose 8% (group 2) and were kept sitting for 3 min after completion of the intrathecal injection of the solution. Patients in group 3 received 3 ml of bupivacaine 0.5% in glucose 8% and were turned into the supine horizontal position immediately after injection. The study was approved by the Ethical Committee of the hospital, and oral consent was obtained from all patients.

Premedication consisted of temazepam 10 mg orally the night before the operation. Before the institution of the spinal anesthesia, 500 ml of Ringer's solution was administered by rapid intravenous infusion. Dural puncture was performed with the patient in the sitting position at the L3–4 interspace by a standard midline or paramedian approach using a 25 gauge spinal needle.

Blood pressure and pulse rate were measured before injection (t = 0) and at 5-min intervals after injection for 20 min (t = 5–20) using an automatic cycling device (Dinamap). ECG was monitored continuously.

Measurement of the height of sensory changes was

Received from the Department of Anesthesiology, Reinier de Graaf Gasthuis, 2625 AD DELFT, The Netherlands. Accepted for publication August 6, 1986.

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Table 1. Characteristics of the Patients Studied

	Group 1 (*n* = 20)	Group 2 (*n* = 20)	Group 3 (*n* = 20)	Δ 1–2	Δ 2–3
Age (yr)	70 ± 1.72	69 ± 1.61	70 ± 1.59	NS	NS
Length (cm)	175 ± 1.36	173 ± 1.47	173 ± 1.90	NS	NS
Weight (kg)	72 ± 1.61	75 ± 2.52	70 ± 2.54	NS	NS

Group 1: plain bupivacaine, 3 min sitting after injection. Group 2: hyperbaric bupivacaine, 3 min sitting after injection. Group 3: hyperbaric bupivacaine, immediately turned to the supine horizontal position.
NS, no statistically significant difference.
Mean values ± SEM.

Table 2. Segmental Levels of Loss of Sensation to Temperature (TEMP) and Pin-Prick (P.PR) 10 and 20 min after Injection

	Group 1 (*n* = 20)	Group 2 (*n* = 20)	Group 3 (*n* = 20)	Δ 1–2	Δ 2–3
TEMP 10′	T-8 (0.7)	T-9 (0.6)	T-10 (0.6)	NS	NS
TEMP 20′	T-7 (0.7)	T-7 (0.6)	T-8 (0.5)	NS	NS
P.PR 10′	T-9 (0.6)	T-10 (0.5)	T-10 (0.3)	NS	NS
P.PR 20′	T-7 (0.6)	T-8 (0.6)	T-9 (0.4)	NS	NS

Groups as defined in Table 1.
NS, not significant.
Mean values ± SEM. SEM in parentheses.

made 10 and 20 min after injection of the bupivacaine solution. Sensory loss was measured in the anterior axillary line by pin prick using a short bevelled 25-gauge needle. Temperature loss was measured using an ice cube. The segment at which the patient was not capable of recognizing the temperature of the ice cube and the segment of loss of sensation to pin prick were recorded. Motor blockade was assessed 10 and 20 min after injection using a 0–3 scale according to Bromage (17). All punctures and observations were made by the authors themselves; the author making the observations concerning levels of blockade and degree of motor blockade was "observer blind", i.e., he did not know whether the patient was in the open group or in the double blind group.

Results are expressed as mean ± SEM. Statistical analysis used the Wilcoxon test for matched pairs for intragroup variations and the Mann-Whitney-*U* test for intergroups comparisons. A *P*-value less than 0.05 was taken as a significant difference.

Results

No significant statistical differences existed among the three groups with regard to age, height or weight (Table 1). The segmental level of temperature loss after 10 min was T-8 in group 1, T-9 in group 2, and T-10 in group 3; after 20 min these levels were T-7, T-7, and T-8, respectively. The segmental level of loss of sensation to pin prick after 10 min was T-9 in group 1, T-10 in group 2, and T-10 in group 3; after 20 min these levels were T-7, T-8, and T-9, respectively. The differences in sensory levels between groups 1 and 2 and between groups 2 and 3 were statistically not significant, at either 10 or at 20 min (Table 2). The ranges of levels are shown in Figure 1. Motor blockade was more intense in the patients who were kept sitting for 3 min (groups 1 and 2), at both 10 and 20 min (Figure 2).

Systolic blood pressures decreased in all groups, with decreases significantly below baseline levels after 5, 10, 15, and 20 minutes in groups 1 and 3; in group 2, decreases were significant after 10, 15 and 20 min. Differences between systolic blood pressures at t = 0 were not significant. Differences between decreases in systolic blood pressures in groups 2 and 3 were not significant at any time; between groups 1 and 2 there was a significant difference between the decreases in systolic blood pressures only after 10 min, at which time the decrease in group 1 was greater.

The decrease in blood pressure was so mild in all patients that vasopressors were not required. In groups 1 and 3 there was a small but not significant decrease in heart rate; in group 2 there was a small increase in heart rate that was significant only at 10 min. Intergroup comparison showed that the differences in changes in heart rates between groups 1 and 2 were significant at 10 min. Hemodynamic data are summarized in Table 3. None of the patients suffered from postspinal headache.

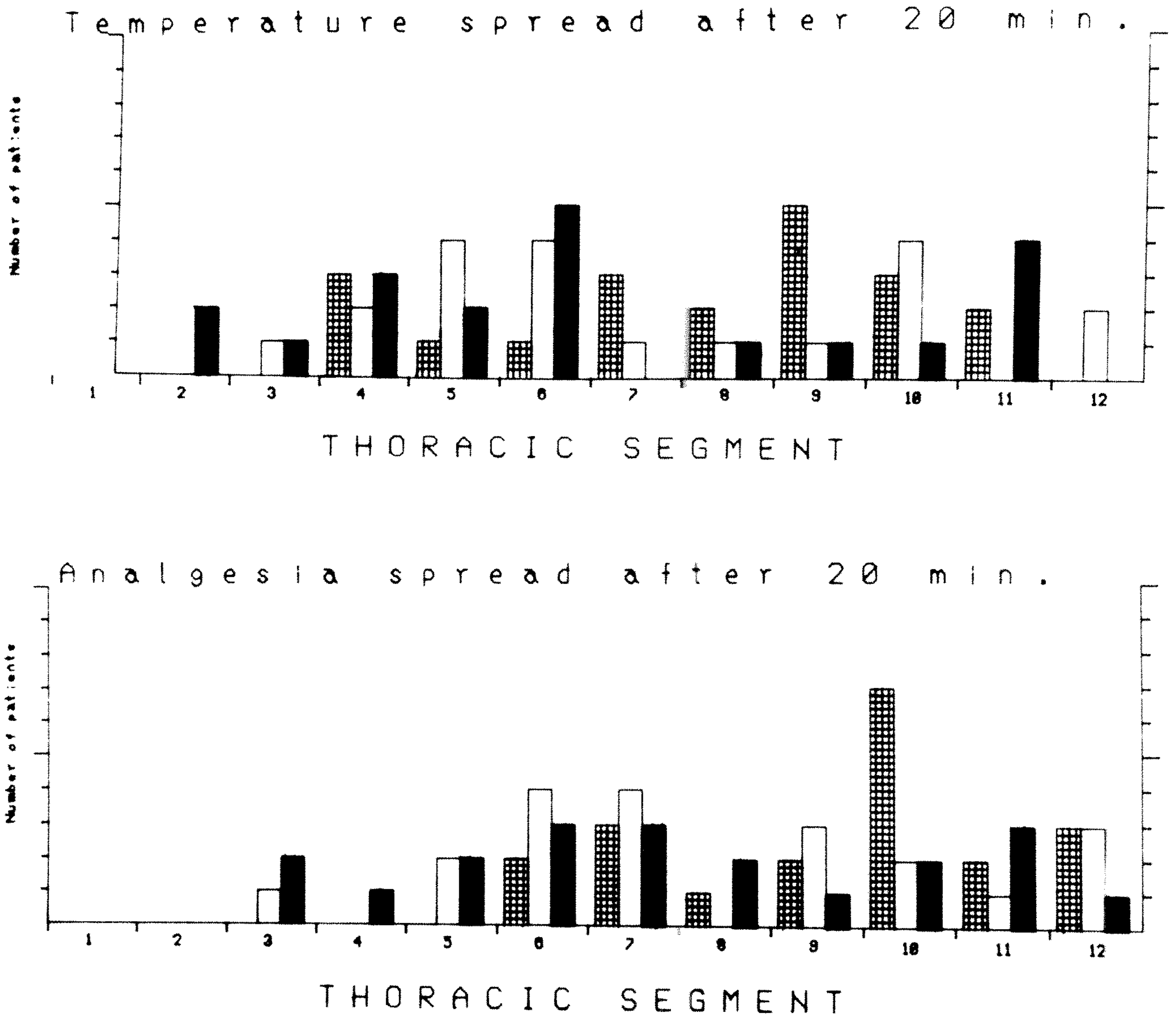

Figure 1. Segmental levels of temperature loss (temperature spread) and loss of sensation to pin-prick (analgesia spread) 20 min after injection. The horizontal axis shows the thoracic segment at which temperature loss and loss of sensation to pin-prick were measured, the vertical axis shows the number of patients.

■ Group 1: plain bupivacaine, 3 min sitting after injection.
□ Group 2: hyperbaric bupivacaine, 3 min sitting after injection.
▦ Group 3: hyperbaric bupivacaine, immediately turned to the supine horizontal position.

Discussion

The factors that govern the spread of intrathecally administered solutions have been and still are subject to speculation. Factors playing a major role have been suggested to be the amount of drug given (9,18) or the volume used (5,19). Speed of injection has been suggested as a factor governing spread but has never been tested; barbotage is believed to increase cephalad spread, although it failed to do so in a controlled study (20). Attention has also focused on the influence of posture and the baricity of the solution. Since the work of Barker (21), who studied the behavior of hyperbaric solutions in a glass tube, local anesthetics for spinal anesthesia have usually been administered as hyperbaric solutions. If the patients are kept in the horizontal position, it has been shown that the use of hyperbaric solutions of tetracaine or bupivacaine result in a higher cephalad spread when compared with the plain solutions (3,13,14,22). However, in a study comparing hyperbaric with isobaric tetracaine in which the patients were kept sitting for approximately 20 sec after injection, there was no difference in cephalad spread (20). Another study reported that

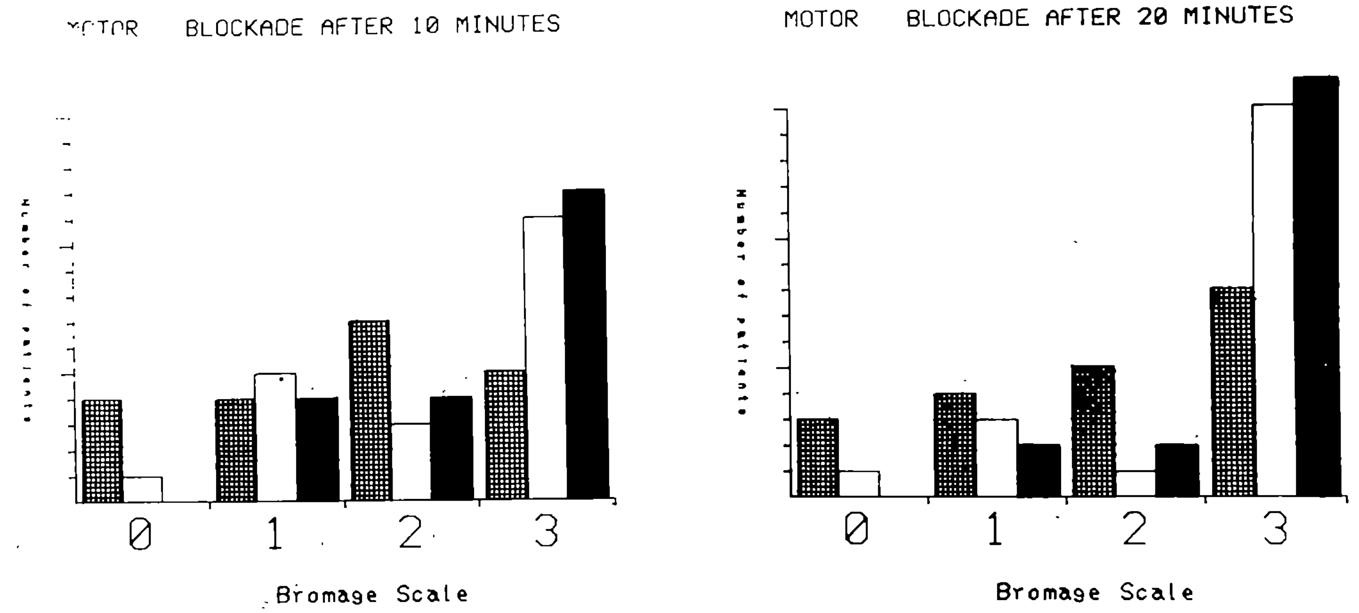

Figure 2. Degree of motor blockade 10 and 20 min after injection. The horizontal axis shows the Bromage scale: 0, no motor block; 1, inability to raise the extended leg; 2, inability to flex the knee; 3, complete motor block. The vertical axis shows the number of patients.
■ Group 1: plain bupivacaine, 3 min sitting after injection.
□ Group 2: hyperbaric bupivacaine, 3 min sitting after injection.
▦ Group 3: hyperbaric bupivacaine, immediately turned to the supine horizontal position.

Table 3. Systolic BP (mm Hg) and Heart Rate (beats/min) at Various Times (t) During and After Injection into Subarachnoid Space

	Group 1	Group 2	Group 3	Δ 1–2	Δ 2–3
Systolic BP (t = 0)	140 (3.32)	142 (2.97)	145 (4.24)	NS	NS
Systolic BP (t = 5)	130 (3.69) $P < 0.01$	140 (3.69) $P = 0$	136 (4.63) $P < 0.05$	NS	NS
Systolic BP (t = 10)	122 (4.63) $P < .001$	135 (4.28) $P < 0.05$	133 (4.55) $P < 0.01$	$P < 0.02$	NS
Systolic BP (t = 15)	122 (3.55) $P < 0.01$	128 (3.61) $P < 0.01$	128 (3.09) $P < .001$	NS	NS
Systolic BP (t = 20)	125 (3.89) $P < 0.01$	129 (4.52) $P < 0.01$	130 (3.29) $P < .001$	NS	NS
Heart rate (t = 0)	75 (3.68)	75 (2.87)	76 (3.14)	NS	NS
Heart rate (t = 5)	76 (3.59) NS	77 (2.96) NS	76 (3.01) NS	NS	NS
Heart rate (t = 10)	75 (3.68) NS	80 (3.55) $P < 0.01$	75 (2.67) NS	$P < 0.05$	NS
Heart rate (t = 15)	74 (3.89) NS	78 (3.08) NS	74 (2.71) NS	NS	NS
Heart rate (t = 20)	74 (3.77) NS	77 (2.89) NS	72 (2.90) NS	NS	NS

Mean values ± SEM (SEM in parentheses).

the cephalad spread of a plain solution of bupivacaine increases if the patient is kept in the sitting position for 2.5 min (23).

It is interesting to see that all authors who consider the plain solution unsuitable, unpredictable, or suitable only for lower limb and perineal surgery perform dural puncture in the horizontal position, turning the patient supine immediately afterwards (3; 12–16). Authors who achieve a good cephalad spread of the plain solution of bupivacaine all perform dural puncture with the patient in the sitting position, keeping the patients sitting for at least 2 min afterwards (9,18,23,24).

In our study, there was no difference in cephalad spread in patients given the hyperbaric and the plain solution in the sitting position. Although this agrees with the results of other studies (18,24), the possibility of a type II error being made must be kept in mind. As can be seen in Figure 1, the variation in cephalad spread is considerable. This could cause masking of an existing significant difference, both between groups 1 and 2 and between groups 2 and 3.

Comparing the sitting patients given hyperbaric bupivacaine with the patients kept horizontal, our study shows that again there was no difference in cephalad spread. This is surprising, because on the basis of baricity one would expect a hyperbaric solution to "sink" in the sitting patient. Indeed, it has been shown that, contrary to common belief, changes in posture cannot be used to control the spread of hyperbaric tetracaine (25) or hyperbaric bupivacaine (26). This suggests that the addition of glucose makes little or no difference with regard to the cephalad spread of an intrathecal solution.

In our study, complete motor blockade was more frequent in the patients kept sitting than it was in patients in the horizontal position; there appeared to be no difference in degree of motor blockade between the patients receiving either the plain or the hyperbaric solution and who were kept sitting for 3 min. In some studies, use of the plain solution has resulted in a higher frequency of complete motor blockade (3,18,24), whereas in other studies this is not so obvious (13,14).

Apart from a significant difference of short duration at 10 min between groups 1 and 2, there were no significant differences with regard to decreases in systolic blood pressure or changes in heart rate, either between groups 1 and 2 or between groups 2 and 3. When performing repeated tests on the same data, there is always a chance of finding a spurious significance; because the aforementioned difference between groups 1 and 2 at 10 min looses significance when Bonferroni's procedure is applied and because a significant difference is not very likely, we feel it is unimportant.

In conclusion, the results of this study indicate that both the plain and the hyperbaric solutions of bupivacaine 0.5% are equally suitable for spinal anesthesia, provided the patients receiving the plain solution are kept in the sitting position for at least 2 min. A possible advantage of the plain solution is that duration of action may be longer. Several studies report that anesthesia using a hyperbaric solution has a shorter duration than anesthesia with a plain solution (13,18,22,25,27), although other studies fail to confirm this (20,24). When using a hyperbaric solution, posture has no influence on cephalad spread under the conditions of the present study. Motor blockade was more intense in the patients who were kept sitting, regardless of the solution used.

References

1. Pflug AE, Aasheim GM, Beck HA. Spinal anesthesia bupivacaine versus tetracaine. Anesth Analg 1976;55:489–92.
2. Moore DC. Spinal anesthesia: bupivacaine compared with tetracaine. Anesth Analg 1980;59:743–50.
3. Chambers WA, Edström HH, Scott DB. Effect of baricity on spinal anaesthesia with bupivacaine. Br J Anaesth 1981;53:279–82.
4. Santos A, Pedersen H, Finster M, Edström H. Hyperbaric bupivacaine for spinal anesthesia in cesarean section. Anesth Analg 1984;63:1009–13.
5. Nolte H, Schikor K, Gergs P, Meyer J, Stark P. Zur Frage der Spinalanaesthesie mit isobarem Bupivacain 0.5%. Anaesthesist 1977;26:33–7.
6. Stra mann D, Gotte A, Meyer-Hamme K, Watermann W. Klinische verlaufe von ueber 6000 spinalanaesthesien mit bupivacain. Regional-anaesthesie 1979;2:49–56.
7. Nightingale PJ, Marstrand T. Subarachnoid anaesthesia with bupivacaine for orthopaedic procedures in the elderly. Br J Anaesth 1981;53:369–71.
8. Tattersall MP. Isobaric bupivacaine and hyperbaric amethocaine for spinal analgesia. A clinical comparison. Anaesthesia 1983;38:115–9.
9. Sheskey MC, Rocco AG, Bizzarri-Schmid M, Francis DM, Edström HH, Covino BG. A dose-response study of bupivacaine for spinal anesthesia. Anesth Analg 1983;62:931–5.
10. Axelsson KH, Edström HH, Widman GB. Spinal anaesthesia with glucose-free 0.5% bupivacaine: effects of different volumes. Br J Anaesth 1984;56:271–8.
11. Bion JF. Isobaric bupivacaine for spinal anaesthesia in acute war injuries. Anaesthesia 1984;39:554–9.
12. Chambers WA. Editorial. Br J Anaesth 1982;54:799–801.
13. Cummings GC, Bamber DB, Edström HH, Rubin AP. Subarachnoid blockade with bupivacaine. Br J Anaesth 1984;56:573–9.
14. Møller IW, Fernandes A, Edström HH. Subarachnoid anaesthesia with 0.5% bupivacaine: effect of density. Br J Anaesth 1984;56:1191–4.
15. Pitkänen M, Haapaniemi L, Tuominen M, Rosenberg PH. Influence of age on spinal anaesthesia with isobaric 0.5% bupivacaine. Br J Anaesth 1984;56:279–84.
16. Logan MR, McClure JH, Wildsmith JAW. Plain bupivacaine: an unpredictable spinal anaesthetic agent. Br J Anaesth 1986;58:292–6.
17. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesthesiol Scand 1965:Suppl 16:55–69.
18. Bengtsson M, Edström HH, Löfström JB. Spinal analgesia with bupivacaine, mepivacaine and tetracaine. Acta Anaesthesiol Scand 1983;27:278–83.
19. Sundnes KO, Vaagenes P, Skretting P, Lind B, Edström HH. Spinal analgesia with hyperbaric bupivacaine: effects of volume of solution. Br J Anaesth 1982;54:69–74.
20. Levin E, Muravchick S, Gold MI. Isobaric tetracaine spinal anesthesia and the lithotomy position. Anesth Analg 1981;60:810–3.
21. Barker AE. A report on clinical experiences with spinal analgesia in 100 cases. Br Med J 1907;1:665–74.
22. Brown DT, Wildsmith JAW, Covino BG, Scott DB. Effect of

baricity on spinal anaesthesia with amethocaine. Br J Anaesth 1980;52:589–95.

23. Kalso E, Tuominen M, Rosenberg, PH. Effect of posture and some c.s.f. characteristics on spinal anaesthesia with isobaric 0.5% bupivacaine. Br J Anaesth 1982;54:1179–84.
24. Krueger D, Iphie P, Nolte H, Edström HH. The effect of glucose concentration on spinal anesthesia with 0.5% of bupivacaine. Reg Anesth. 1983;6:1–3.
25. Wildsmith JAW, McClure JH, Brown DT, Scott DB. Effects of posture on the spread of isobaric and hyperbaric amethocaine. Br J Anaesth 1981;53:273–8.
26. Sinclair CJ, Scott DB, Edström HH. Effect of the Trendelenberg position on spinal anaesthesia with hyperbaric bupivacaine. Br J Anaesth 1982;54:497–500.
27. Gray DC, Carel WD, Smith TC. Effects of density of solution on extent of subarachnoid block. Anesthesiology 1980;53:S–234.

ANESTH ANALG
1987;66:177–80

The Lumbar Subdural Extraarachnoid Space of Humans:
An Anatomical Study Using Spinaloscopy in Autopsy Cases

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BLOMBERG RG. The lumbar subdural extraarachnoid space of humans: an anatomical study using spinaloscopy in autopsy cases. Anesth Analg 1987;66:177–80.

The lumbar subdural extraarachnoid space was examined by spinaloscopy in 15 autopsy subjects. Special attention was paid to the ease with which the space opened up and also to the extent of view achieved. In ten cases the space opened up with ease, in four cases with difficulty, and in one case it was not possible to establish the subdural space at all. The bevel of an 18-gauge Tuohy needle introduced into the subdural space could be visualized in eight of 13 cases. An epidural catheter was then passed through the Tuohy needle into the subdural space in eight cases and was visualized in six of them. Although care must be exercised in drawing conclusions for clinical epidural anesthesia from autopsy cases, this study confirms the possibility of placing both the bevel of a Tuohy needle and an epidural catheter in the subdural space. The results reemphasize the need for caution suggested by other reports regarding the possibility of subdural puncture in epidural anesthesia and subsequent injection of anesthetic solution into the subdural space.

Key Words: ANATOMY—spinal canal, subdural space. ANESTHETIC TECHNIQUES—spinal, epidural.

Accidental subdural extraarachnoid puncture as a complication of epidural anesthesia was radiologically demonstrated in 1975 by Boys and Norman (1) and since then by several other authors (2–5). Mehta and Maher described deliberate therapeutic subdural puncture in 1977 (6).

In 1985, Mehta (7) reported a series of 100 extradural anesthetic blocks performed by trained anesthesiologists and showed with radiologic technique that the position of the Tuohy needle was partially subdural in seven cases. Subdural puncture may thus occur in epidural anesthesia even in experienced hands. However, the patency of the lumbar subdural space has not been studied. With the aim of demonstrating the subdural space in a situation as similar as possible to that of clinical epidural anesthesia, the technique of spinaloscopy was used on autopsy subjects. In 1985 I described the method (8), unfortunately then unaware of the work of Ooi et al. (9–11), which was thus not given due credit. Since 1967, Ooi et al. have reported on the use of spinaloscopy in 208 patients, with particular emphasis on observations of the cauda equina and herniated discs. The technique in this present study differs in using an endoscope with a 90° lens and in carefully injecting air in order to open the epidural and subdural spaces.

Methods

Spinaloscopy was performed on 15 autopsy subjects aged 47–83 yr. The age and sex of the subjects are presented in Table 1. All findings were documented by photography.

Spinaloscopy was performed with a rigid needle arthroscope, the Olympus Selfoscope. For this study the larger model, SES 2211 S, was used. It has an external diameter of 2.2 mm. It is equipped with a wide-angle Selfoc lens at the tip that is directed 90° to the longitudinal axis, together with a window for emission of light transmitted from a light source, the Olympus CLV-10, by an optic cable. For photography the endoscope was attached to an Olympus OM-2 camera with an adapter that gives a magnification equivalent to that of a 105 mm lens.

The epidural space was first located with an 18-gauge Tuohy needle by loss of resistance to air in the lumbar interspace L3-4 using the midline approach in all cases but one (case 15), where the paramedian

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This study has been supported by grants from the Swedish Society of Medicine, the Fredga Research Foundation and the County Council of Östergötland, Sweden. Presented in part at the General Assembly of the Swedish Society of Medicine in Stockholm, November 27, 1985.

Received from the Department of Anesthesia, Central Hospital, Norrköping, and the Department of Anesthesiology, Linköping University Hospital, Linköping, Sweden. Accepted for publication September 10, 1986.

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Table 1. Age and Sex Distribution of 15 Autopsy Subjects on whom Spinaloscopy Was Performed

Age group (yr)	Men	Women	Total
40–49	1	—	1
50–59	—	1	1
60–69	3	1	4
70–79	7	1	8
80–89	—	1	1
Total	11	4	15

technique was used. The endoscope was then introduced with the aid of a trocar and a sheath in the lumbar interspace L2-3. In two cases the examination was ultimately performed one level (case 11) and two levels (case 7) cephalad to the first interspaces because of difficulties encountered. After visual identification of the epidural space the endoscope was advanced into the subarachnoid space with the aid of trocar and sheath. The pressure of the cerebrospinal fluid was measured whenever spontaneous flow through the sheath of the endoscope occurred.

The subarachnoid space was flushed with saline through the sheath of the endoscope to improve visibility through the scope and facilitate inspection of the contents of the subarachnoid space, mainly nerve roots of cauda equina and the corresponding vessels (Fig. 1). With continued careful flushing through the sheath, the endoscope was then slowly withdrawn until the subdural space was encountered (Fig. 2). A complete opening was identified by the thin arachnoid membrane suddenly covering and blurring the nerve roots, which could still be faintly seen through the membrane. The subdural space could clearly be distinguished from the epidural space as described in a study performed with epiduroscopy (12).

In 13 subjects a Tuohy needle inserted one lumbar interspace caudad to the endoscope was then advanced into the established subdural space and saline injected through the needle to further open up the space (Fig. 3). Finally, in eight cases an epidural catheter (Vygon, external diameter 1.0 mm) was introduced through the Tuohy needle into the subdural space.

The ease with which the subdural space could be opened up by injection of saline was recorded. Also, the extent of view into the subdural space, defined by visualization of the Tuohy needle one lumbar space away, was noted.

Hospital records of all subjects were examined for information about factors that might be suspected of influencing relationships in the subdural space and surrounding tissues. Such factors included diagnostic lumbar puncture, subarachnoid and epidural anesthesia, and spinal pathology of any sort.

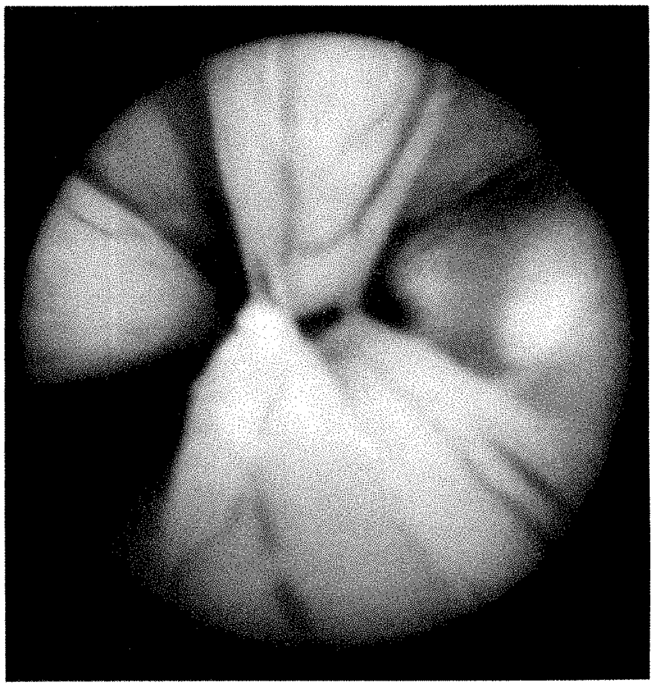

Figure 1. Spinaloscopy (case 12). The nerve roots of the cauda equina. Caudad view, ventral to left, dorsal to right.

Results

A summary of the results is presented in Table 2. Of the 15 autopsy subjects the subdural space was easily opened in ten. In four cases the space was exposed with difficulty, and in one case it was not possible to establish the space at all. No relationship was found between the ease with which the space was opened and the time period that had elapsed between death and endoscopic examination.

The bevel of the Tuohy needle located one lumbar interspace caudad to the endoscope (roughly 2.5–3 cm) was seen in eight of the 13 cases where the needle was advanced into the subdural space. In the remaining five cases technical difficulties, mainly folds of arachnoid membrane, obstructed the view. However, the presence of the needle was indicated by widening of the space as saline was injected through the needle.

An epidural catheter was introduced through the Tuohy needle into the subdural space in eight subjects and was visualized in six of them. As the catheter

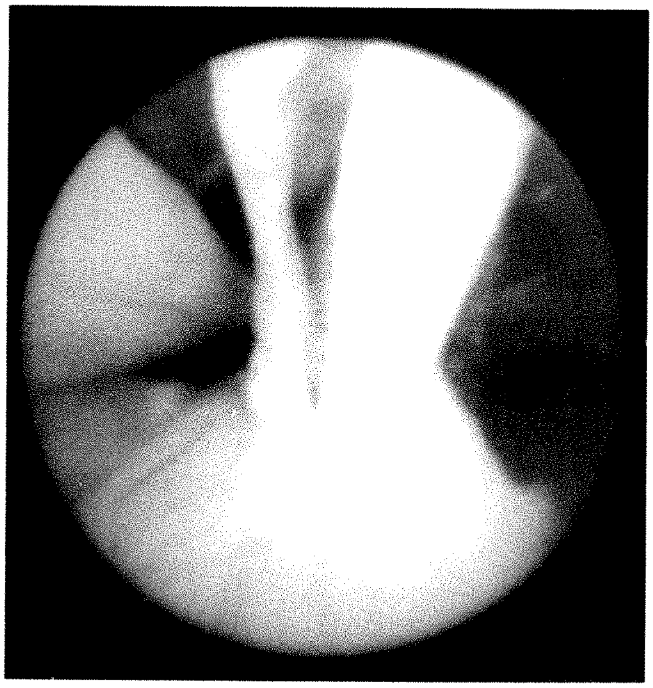

Figure 2. Spinaloscopy (case 12). Partial opening of subdural space. Caudad view, ventral to left and dorsal to right. From left to right can be seen the nerve roots in the subarachnoid space, the thin arachnoid membrane, the subdural space partially opened, and the thick dura mater. To far right, the epidural space can be seen.

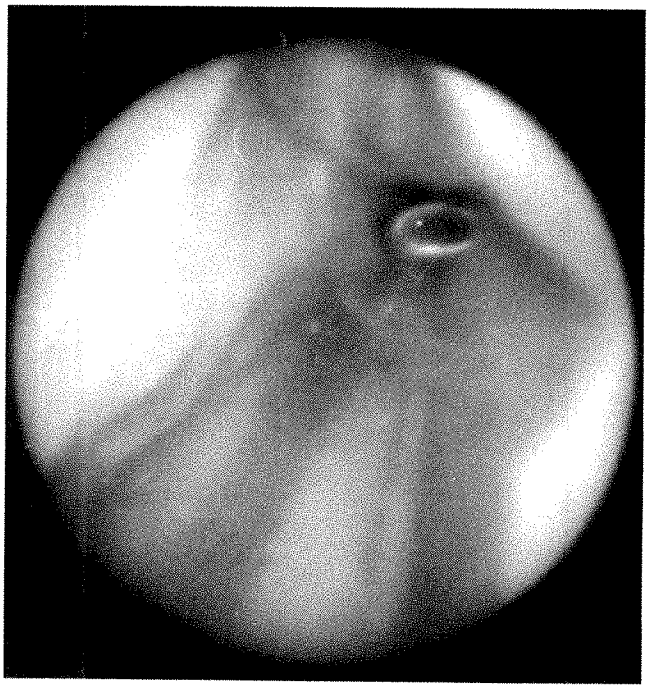

Figure . Spinaloscopy (case 10). Subdural space fully opened, containing bevel of 18-gauge Tuohy needle (length of orifice, 2.0 mm). Caudad view, ventral to left and dorsal to right. The nerve roots to left are covered by folds of arachnoid membrane. The dura mater is to the right.

was advanced it was seen to further widen the subdural space. The catheter perforated the arachnoid membrane in one case (case 13) and entered the subarachnoid space.

The pressure of the cerebrospinal fluid when the sheath initially entered the subarachnoid space was nil in 13 cases (examined 10 hr after death or later), 7 cm H_2O in case 12 (examined 7 hr after death) and 5 cm H_2O in case 13 (examined 4 hr after death). Watertight conditions were not always possible and leaks were frequent; conditions for measurement of pressures and injected volumes were thus not favorable. However, in one case (case 5) it was possible to perform a successful measurement of CSF through a separate needle after injection of saline into the subarachnoid space when it was first entered. Cerebrospinal fluid pressure was recorded as 11 cm H_2O at the same time as the subdural space was opened.

The hospital records of the 15 subjects showed that previous diagnostic lumbar puncture had been performed in three cases, subarachnoid anesthesia in two cases, and epidural anesthesia in four cases (Table 2). In one subject (case 14) both subarachnoid anesthesia and a diagnostic lumbar puncture had been performed. These previous events were included regardless of time of occurrence.

Discussion

The clinical conclusions that may be drawn from autopsy cases are limited because several factors affecting the subdural space differ antemortem and postmortem. One of these is the very low pressure of the cerebrospinal fluid present at the time of examination that might facilitate opening of the subdural space. However, in this study it was shown in one case that even a pressure of 11 cm H_2O in the subarachnoid space did not prevent easy separation of the arachnoid membrane from the dura mater.

As might be expected, the two cases with initially measurable cerebrospinal fluid pressure were studied relatively shortly after death. In the remainder of the material the time lapse between death and spinaloscopy was sufficient for cerebrospinal fluid pressure to decrease to atmospheric pressure.

Absence of blood flow in the epidural space will presumably reduce the volume of the epidural space. Also, a certain amount of postmortem autolysis cannot be excluded. Finally, introduction of trocar, sheath, and endoscope may traumatize the dura mater and the arachnoid. All these factors might facilitate separation of the arachnoid from the dura mater.

This limited study has shown that it is possible to

Table 2. Results of Spinaloscopy in 15 Autopsy Subjects

Case number	Age/sex	Opening of subdural space	Tuohy needle	Catheter	Remarks
1	62 yr/M	Easy	Seen	Seen	Epidural anesthesia in 1958
2	77 yr/M	Easy	Not seen	—	Epidural anesthesia in 1983
3	70 yr/M	Easy	Seen	Seen	Epidural anesthesia twice in 1978
4	76 yr/M	Easy	Not seen	—	Lumbar puncture in 1985
5	79 yr/M	Easy	Seen	—	—
6	63 yr/M	Easy	Seen	Seen	Lumbar puncture in 1981
7	76 yr/M	Difficult (Th12-L1)	—	—	Subarachnoid anesthesia in 1958
8	60 yr/M	Easy	Not seen	—	—
9	55 yr/F	Not established			—
10	68 yr/F	Easy	Seen	Seen	—
11	83 yr/F	Difficult (L1-2)	Not seen	Not seen	—
12	71 yr/M	Difficult	Not seen	Not seen	Epidural anesthesia in 1979
13	74 yr/M	Difficult	Seen	Seen	—
14	73 yr/F	Easy	Seen	Seen	Subarachnoid anesthesia in 1950; lumbar puncture in 1976
15	47 yr/M	Easy	Seen	—	—

demonstrate the lumbar subdural space in autopsy cases by means of spinaloscopy and to confirm that the subdural space is capable of accepting the bevel of a Tuohy needle as well as an epidural catheter. The subdural space was easily opened in ten subjects. In the four cases where difficulties were encountered and in the one case where it was not possible to establish the subdural space the cause of the difficulties could not be determined by spinaloscopy. There was no relation between the problems in these five cases and earlier diagnostic or therapeutic procedures such as lumbar puncture, subarachnoid and epidural anesthesia.

Even though conclusions regarding clinical epidural anesthesia must be drawn with care, these results indicate that during subarachnoid or epidural anesthesia caution is necessary to avoid subdural puncture with subsequent injection of anesthetic solution into the subdural extraarachnoid space.

The endoscope and camera equipment were supplied by Astra Läkemedel AB, who also generously contributed to the light source. This study was made possible by the kind cooperation of the staffs of the Department of Pathology, Central Hospital, Norrköping, and the Department of Forensic Medicine, Linköping University Hospital.

References

1. Boys JE, Norman PF. Accidental subdural analgesia. Brit J Anaesth 1975;47:1111–3.
2. Manchanda VN, Murad SHN, Shilyansky G, Mehringer M. Unusual clinical course of accidental subdural local anesthetic injection. Anesth Analg 1983;62:1124–6.
3. Brindle Smith G, Barton FL, Watt JH. Extensive spread of local anaesthetic solution following subdural insertion of an epidural catheter during labour. Anaesthesia 1984;39:355–8.
4. Stevens RA, d'Arcy Stanton-Hicks M. Subdural injection of local anesthetic: a complication of epidural anesthesia. Anesthesiology 1985;63:323–6.
5. Hartrick CT, Pither CE, Umeshraya P, Raj PP, Tomsick TA. Subdural migration of an epidural catheter. Anesth Analg 1985;64:175–8.
6. Mehta M, Maher R. Injection into the extra-arachnoid subdural space. Anaesthesia 1977;32:760–6.
7. Mehta M. Extradural block. Confirmation of the injection site by X-ray monitoring. Anaesthesia 1985;40:1009–12.
8. Blomberg R. A method for epiduroscopy and spinaloscopy. Acta Anaesthesiol Scand 1985;29:113–6.
9. Ooi Y, Satoh Y, Morisaki N. Myeloscopy: possibility of observing lumbar intrathecal space by use of an endoscope. Endoscopy 1973;5:91–6.
10. Ooi Y, Satoh Y, Sugawara S, Mikanagi K, Morisaki N. Myeloscopy. Int Orthop 1977;1:107–11.
11. Ooi Y, Satoh Y, Inoue K, Mikanagi K, Morisaki N. Myeloscopy with special reference to blood flow changes in the cauda equina during Lasègue's test. Int Orthop 1981;4:307–11.
12. Blomberg R. The dorsomedian connective tissue band in the lumbar epidural space of humans. Anesth Analg 1986;65:747–52.

ANESTH ANALG
1987;66:181–4

Effects of 100% Oxygen and a Mixture of Oxygen and Air on Oxygen Saturation in the Immediate Postoperative Period in Children

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VIJAYAKUMAR HR, METRIYAKOOL K, JEWELL MR. Effects of 100% oxygen and a mixture of oxygen and air on oxygen saturation in the immediate postoperative period in children. Anesth Analg 1987;66:181–4.

Arterial oxygen saturation during transportation of children from the operating room to the recovery room and in the recovery room was monitored in two groups of patients, one given 100% oxygen at the end of anesthesia, the other given a 50:50 mixture of oxygen and air. The oxygen–air group had a statistically significantly higher incidence of hypoxemic episodes. Preoxygenation with 100% oxygen before transfer from the operating room reduces the incidence of hypoxemia in children.

Key Words: ANESTHESIA—pediatric. OXYGEN—saturation. RECOVERY—oxygen saturation.

General anesthesia is known alter Arterial oxygenation. Reduction in functional residual capacity (FRC), closure of small airways, and associated ventilation–perfusion imbalance are among the causes of hypoxemia under anesthesia. Each of these can continue well into the postoperative period (1–3, 14). In addition, pain caused by upper abdominal incisions, central respiratory depression caused by narcotics or inhalational anesthetics, residual muscle paralysis, diffusion hypoxemia caused by rapid elimination of nitrous oxide, shivering, coughing, breath holding, and airway obstruction can all cause hypoxemia in the postoperative period. It is a common practice among anesthesiologists to give high concentrations of oxygen while anesthesia is being terminated. This is usually done with the idea of preventing diffusion hypoxemia and to create a reserve of oxygen in alveolar air during transport.

It has also been recommended that a mixture of oxygen and air be given towards the end of surgery to avoid atelectasis and increased intrapulmonary shunting caused by the rapid resorption of oxygen when 100% oxygen is administered at the end of an anesthetic. Most anesthesiologists at Children's Hospital of Michigan use a 50:50 mixture of oxygen and air towards the end of surgery although some prefer to use 100% oxygen.

This study was conducted to compare the effects of different inhaled concentrations of oxygen at the conclusion of an anesthetic and to examine other factors that might influence arterial oxygen saturation immediately after anesthesia. Oxygen saturation was measured by a pulse oximeter (Nellcor) that has a rapid response, is noninvasive, and is based on the principles of spectrophotometry and plethysmography.

Methods

One hundred and one cases were included in the study. Ages ranged from 2 months to 17 yr (mean 64.7 months). Sixty-two cases were ASA physical status I, thirty-six were status II and three cases were status III. All patients were scheduled for elective procedures, primarily eye muscle corrections, hernia repairs, or orthopedic operations. No patient had an abdominal or thoracic operation. Anesthesia was induced by inhalational agents intravenous thiopental, or intramuscular methohexital. Maintenance of anesthesia was with nitrous oxide, oxygen, and one of the three halogenated agents—halothane, enflurane, or isoflurane. Toward the end of the operation the nitrous oxide was turned off and patients were given either 4 L/min flow of 100% oxygen (group 1) or 2 L/min oxygen and 2 L/min air (group 2) depending upon which of the two randomly allocated groups the

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Received from the Department of Anesthesiology, Children's Hospital of Michigan, Detroit, Michigan. Accepted for publication September 12, 1986.

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patients had been assigned to. The concentration of oxygen in the oxygen–air mixture was between 59 and 62%, as measured by an oxygen analyser (Oxycheck–Critikon). The deviation of administration of these gas mixtures was noted as the "nitrous oxide elimination time." In most cases this was at least 3 min. At the end of the operation the patients were either extubated on the operating table before responding to the tube or were transported to the recovery room to be extubated when fully awake. All patients were transported while breathing room air. Almost all patients were extubated in the operating room except those who were less than 6 months old and those who had potential upper airway obstruction.

A pulse oximeter was used to measure the oxygen saturation every 30 sec from the time nitrous oxide was turned off until 3 min after breathing added O_2 in the recovery room. During transport, the pulse oximeter was placed on the foot end of the cart and its display was turned away from the anesthesiologist in charge of the patient. An independent observer recorded the oxygen saturation. It was up to the anesthesiologist (the first author) at the head of the patient to manage the airway appropriately based on clinical judgement only. The mean time taken for transport from the operating table to recovery room was 1 min 49 sec. Comments were written based on the clinical impressions of the anesthesiologist as to whether the transport was smooth, whether the patient reacted to the endotracheal tube (coughing or breath holding), or whether the patient was mildly obstructed (snoring). In the recovery room all patients were given 5 L/min of oxygen through a loosely fitting face mask. The rare occurrence of partial laryngeal spasm was treated with oxygen under positive pressure.

The data were analyzed by a microcomputer with the help of the Statistical Package for Social Sciences (SPSS). One-way and two-way analysis of variance and χ^2 analysis were made to determine the levels of statistical significance. The following variables were used for statistical analysis:

1. The lowest recorded oxygen saturation (SaO_2) during the period of observation.
2. Lowest saturation during transportation
3. Lowest saturation in recovery room
4. "Percentage decrease," which is:

$$\frac{(\text{Highest Saturation} - \text{Lowest Saturation})}{\text{Highest Saturation}} \times 100$$

5. Oxygenation Status:
   Normoxemia (SaO_2 of 90% and above);
   Hypoxemia (SaO_2 89% and lower)

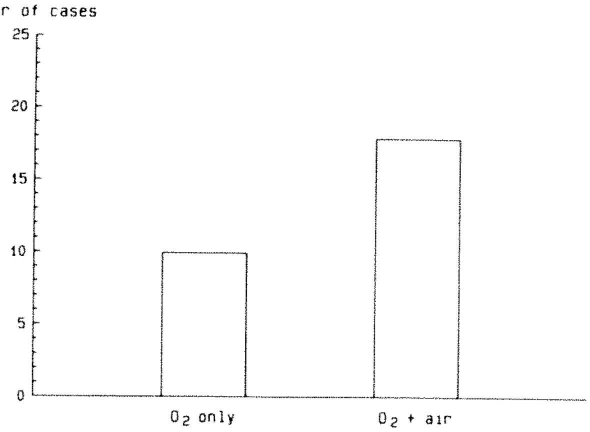

Figure 1. Incidence of hypoxemia.

Results

Fifty-two cases were given 100% oxygen (group 1) and 49 were given oxygen and air (group 2) before transport. Twenty-eight of the total 101 cases had oxygen saturations of less than 90%. Ten of the twenty-eight 'hypoxemic' cases were in group 1; eighteen were in group 2 (Fig. 1). This difference was statistically significant ($P = 0.049$). Mean lowest saturation was 91.4% in group 1 and 87.36% in group 2. Mean lowest saturation during transport 93.32% in group 1 was and 89.04% in group 2. Percentage decrease in oxygen saturation in group 2 was greater than group 1, but the difference was not statistically significant. Oxygen saturations returned to nearly equal levels when supplemental oxygen was started in the recovery room (Table 1).

Twenty-five cases in group 1 were ASA physical status I and had smooth transport. One of these 25 became hypoxemic. The remaining 24 normoxemic cases had a mean lowest saturation of 95.4% (Table 2). Twenty-one cases in group 2 were ASA-I and one became hypoxemic. The remaining 20 had a mean lowest saturation also of 95.5%.

Oxygen desaturation was not related to age, ASA physical status, or the time during transport when it occurred. Whether or not an endotracheal tube was in place during transport did not influence the lowest recorded oxygen saturation. The two factors yielding the greatest decrease in oxygen saturation were primarily a "nonsmooth" transport ($P = 0.00$), and secondarily, coexisting disease ($P = 0.019$).

Thirty cases in the entire sample had either reacted to the endotracheal tube, coughed, or snored. Nineteen of them became hypoxemic (Table 2).

An interesting observation was made about the relationship between postoperative oxygen saturation and coexisting diseases. Mean lowest saturations of

Table 1. Arterial Oxygen Saturations

	Lowest saturation (mean)	Lowest saturation during transport (mean)	Lowest saturation in PAR with O_2	Percentage drop (mean)	SaO_2 89 and lower
Group 1	91.4	93.32	94.76	8.28	10
Group 2	87.36	89.04	94.77	12.41	18

Abbreviation: PAR, postanesthetic recovery.

Patients in group 1 received 100% oxygen for 3 min prior to leaving the operating room; patients in group 2 were given oxygen plus room air (50% O_2, 50% N_2).

Table 2. Incidence of Hypoxia during Transport

	Total cases	Cases with "nonsmooth" transport[a]	Number of cases in ASA I and with smooth transport[a]	Mean lowest SaO_2 in ASA I patients with smooth transport
Group 1	52	15(9)	25(1)	95.4%
Group 2	49	15(10)	21(1)	95.5%

[a] Numbers in brackets indicate the number of hypoxemic cases ($O_2 < 90\%$).

Table 3. Cases with Coexisting Diseases

	Lower airway problems	Upper airway problems	Ex-premature children	Obesity	Cardiac problems	Others
Group 1	2(1)	4(1)	2(0)	2(1)	1(1)	8(0)
Group 2	5(3)	3(1)	5(4)	1(1)	1(0)	5(1)

Numbers in brackets indicate the number of hypoxemic cases ($SaO_2 < 90\%$).

less than 85% were associated with lower airway disorders, ex-premature status, and obesity (Table 3, Figs. 2 and 3). The statistical significance of any of these observations could not be determined because of the small number of cases in each group and the wide scatter of values around the mean lowest oxygen saturation.

Discussion

Arterial oxygen saturation in the immediate postoperative period has been studied recently using a pulse oximeter (4,5). This noninvasive rapid response method of measuring arterial oxygen saturation is becoming increasingly popular and its accuracy has been established (6).

During anesthesia, the alveolar–arterial oxygen gradient increases due to changes in lung volume and ventilation–perfusion mismatches (1). The increased venous admixture may be caused by maldistribution of ventilation and perfusion and/or frank shunting across collapsed alveoli. The decrease in FRC and the increase in closing volumes ordinarily associated with general anesthesia are further exaggerated because of a low elastic recoil of the thorax and lungs in children (7). When closing volume exceeds FRC, the gases trapped beyond the closed terminal bronchioli are absorbed leading to alveolar collapse. Nitrogen, which is relatively less soluble in blood than either oxygen or nitrous oxide, can be assumed to greatly delay this process of alveolar collapse.

There are several studies that report increased intrapulmonary shunting after ventilation with 100% oxygen (8–13). One possible mechanism by which this can occur is resorption atelectasis. Another is oxygen-induced pulmonary vasodilatation that increases blood flow through nonventilated hypoxic segments (14). Inhaled air or nitrogen maintains lung volume by delaying resorption of trapped gases.

Identical oxygen saturations were seen in the present study in ASA I patients with smooth transport in both groups. We believe this confirms the concept that resorption atelectasis is not the most likely source of oxygen desaturation immediately after anesthesia.

The opportune moment for leaving the operating room was based on clinical judgement; nevertheless, a 30% incidence of coughing, light snoring, or breath holding occurred during transport. Our study shows

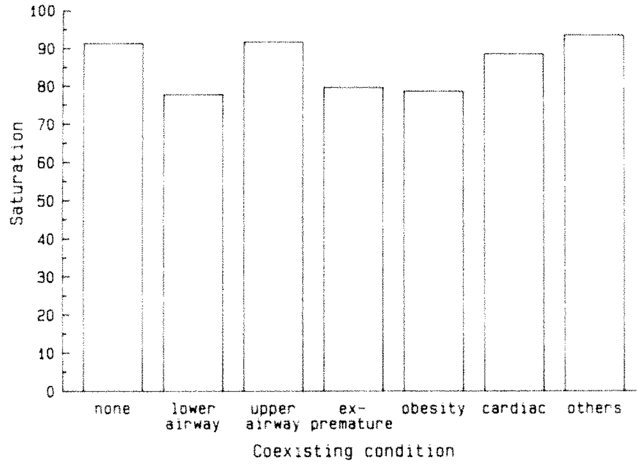

Figure 2. Lowest saturation.

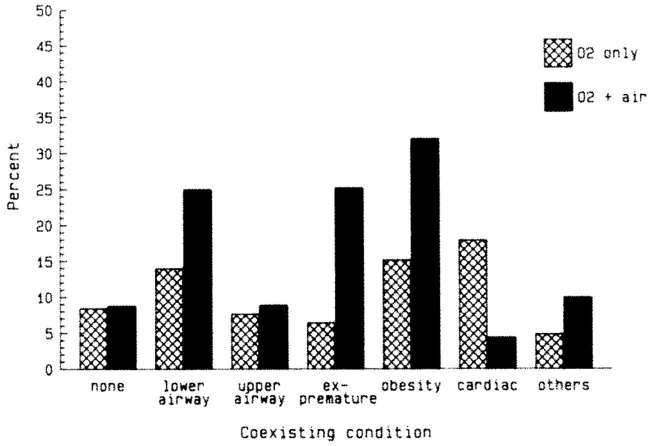

Figure 3. Percentage decrease in oxygen saturation.

that these events have a measurable effect on oxygen saturation. Patients in group 1, who had 100% oxygen, had fewer hypoxic episodes, probably because of the larger reserve of oxygen in alveolar air.

Greater oxygen desaturation tended to occur in the presence of coexisting diseases such as lower airway disorders, prematurity, or obesity. Though the statistical significance could not be determined in this study, a more controlled experiment is indicated to identify factors that increase risk of hypoxemia during transport to the recovery room. The seven cases with lower airway disorders included four cases with asthma, one with cystic fibrosis, and one with suspected pulmonary tuberculosis; one of the seven had had bronchitis 1 month previously.

We conclude that any event interrupting smooth postanesthesia ventilation can rapidly result in significant hypoxemia. Our data indicate that it is best for pediatric patients to have 100% oxygen prior to transfer from the operating table to the recovery room. The benefits of nitrogen as a diluent are not demonstrable, at least in the immediate postanesthetic period, and use of nitrogen increases the risk of hypoxia in patients for whom transport to the recovery room was not entirely smooth, as well as in patients with coexisting diseases.

The authors thank Ms. Karen Olson for technical assistance and Ms. Susan Nast for preparation of the manuscript.

References

1. Marshall BE, Wyche MQ. Hypoxemia during and after anesthesia. Anesthesiology 1972;37:178–209.
2. Spence AA, Alexander JL. Mechanisms of postoperative hypoxaemia. Proc Roy Soc Med 1972;65:12–14.
3. Marshall BE, Cohen PJ, Klingenmaier CH, Aukberg S. Pulmonary venous admixture before during and after halothane: oxygen anesthesia in man. J Appl Physiol 1969;27:653–7.
4. Tyler IL, Tantisiva B, Winter PM, Motoyama EK. Continuous monitoring of arterial oxygen saturation with pulse oximetry during transfer to the recovery room. Anesth Analg 1985;64:1108–12.
5. Motoyama EK, Glazener CH. Hypoxemia after general anesthesia in children. Anesth Analg 1986;65:267–72.
6. Yelderman M, New W, Jr. Evaluation of pulse oximetry. Anesthesiology 1983;59:349–52.
7. Motoyama EK, Cook CD. Respiratory physiology. In: Smith RM ed. Anesthesia for infants and children. 4th ed. St. Louis: CV Mosby. 1980.
8. Kerr JH, Foex P, Pybus DA. Relationships between inspired oxygen concentration and venous admixture during nitrous oxide–oxygen–halothane anaesthesia. Br J Anaesth 1985;57:1150–60.
9. Drummond GB, Wildsmith JAW, Masson AHB. Impairment of oxygen transfer in the lung by increasing oxygen concentration during halothane and trichloroethylene anaesthesia. Br J Anaesth 1978;50:255–60.
10. Wagner PD, Laravuso RB, Uhl RR, West JB. Continuous distribution of ventilation–perfusion ratios in normal subjects breathing air and 100% O_2. J Clin Invest 1974;54:54–68.
11. Douglas ME, Downs JB, Dannemiller FJ, Hodges MR, Munson ES. Pulmonary venous admixture. Anesth Analg 1976;55:688–95.
12. Quan SF, Kronberg GM, Schlobohm RM, Feely TW, Don HF, Lister G. Changes in venous admixture with alterations of inspired oxygen concentration. Anesthesiology 1980;52:477–82.
13. Suter PM, Fairley HB, Schlobohm RM. Shunt lung volume and perfusion during short periods of ventilation with oxygen. Anesthesiology 1975;43:617–27.
14. Smith RM. Anesthesia for infants and children under one year of age. In: Smith RM, ed. Anesthesia for infants and children. 4th ed. St. Louis: CV Mosby, 1980:291.

ANESTH ANALG
1987;66:185–7

Technical Communication

Capnogram Artifact during High Airway Pressures Caused by a Water Trap

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Capnograms are useful in monitoring mechanical ventilation (1). During ventilation with a partially obstructed endotracheal tube resulting in elevated airway pressure (Paw), we recently observed unexpected CO_2 waveforms. The capnogram falsely indicated a brief period of expiration during mechanical inspiration (Fig. 1). A 30-ml water trap between the sampling tube and the capnograph was considered to be the origin of the CO_2 measured during inspiration. This report describes a laboratory investigation of this problem.

Methods

One bellows of a modified test lung (Vent Aid, Michigan Instruments, Grand Rapids, MI) (2) was used to simulate the lungs. Compliance was set at 0.1 L/cm H_2O. A cuffed, 8-mm inner diameter endotracheal tube was inserted into the model's "trachea" (Imatrach, Adult Tracheal Model, National Catheter Co.). The resulting airway resistance was 2.5 L/cm H_2O. One hundred percent carbon dioxide was infused into the lungs at a rate of 200 ml/min, approximating normal CO_2 production in adults. The test lung was ventilated with an electronic ventilator (Ohio 7000, Ohio Medical Products, Madison, WI) by means of an anesthesia machine (Ohio Modulus 1) with a circle system.

Carbon dioxide tension, Paw, and flow rate in the airway were measured at the junction between the endotracheal tube and the breathing circuit. The capnogram was recorded with a Datascope Accucap (Datascope Corp., Paramus, NJ). Airway pressure was measured with an electronic transducer (Statham-Gould PM 131 TC) and flow rate with a Fleisch pneumotachograph (Dynasciences, Blue Bell, PA). Carbon dioxide tension, pressure, and flow waveforms were recorded on a multichannel, polygraph amplifier–recorder (Grass Medical Instruments, Quincy, MA). Steady state ventilation was established at a respiratory rate of 6/min with a tidal volume of 1000 ml and a fresh gas flow rate of 5 L/min; Paw was 12 cm H_2O.

To investigate the effect of Paw on measurements of P_{CO_2} during inspiration, the endotracheal tube was partially obstructed with a surgical clamp; the obstruction was varied to produce Paw from 20 to 60 cm H_2O in increments of 10 cm H_2O. Airway pressure was then established at a baseline of 50 cm H_2O by adjusting the clamp. Recordings at this baseline Paw were made first with the water trap attached to the capnograph and then with the water trap bypassed. Recordings were then made with the effective water trap volume, initially 30 ml, reduced by the addition of water in increments of 5 ml. The influence of respiratory rate was investigated at 8/min and 12/min.

Inspiratory P_{CO_2} was related to Paw and began to be reflected in the waveform when Paw was 30 cm H_2O (Fig. 2). Both the amplitude and the duration of the effect increased when Paw increased. When the water trap was bypassed, the effect did not occur (Fig. 3). As the volume of the water trap was reduced, the P_{CO_2} became progressively smaller (Fig. 3). The artifact virtually disappeared after the addition of 20 ml of water; thus, the effective volume in the water trap at that time was 10 ml.

Discussion

A large water trap attached to a capnograph during sampling can produce artifacts at high Paw. The capnograph water trap is situated at the end of the sam-

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Received from the Department of Anesthesiology, University of Florida College of Medicine, Gainesville, Florida. Accepted for publication September 2, 1986.

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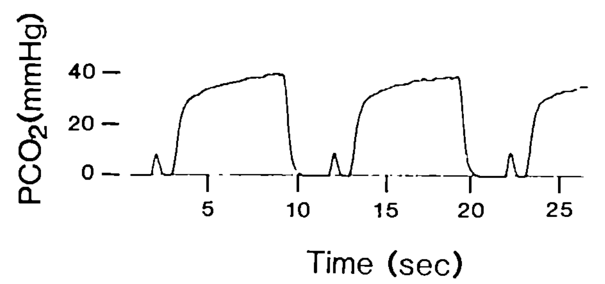

Figure 1. Capnograms during mechanical ventilation. The endotracheal tube was partially obstructed and peak pressure in the circuit was 50 cm H_2O. The waveforms indicate a brief expiraticn during mechanical inspiration.

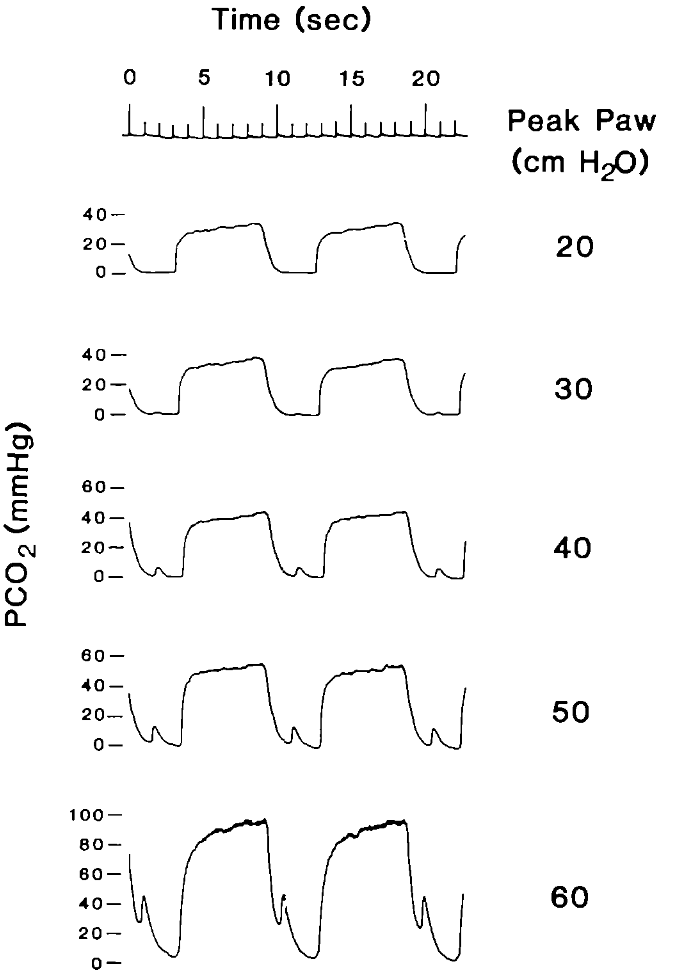

Figure 2. Capnograms showing CO_2 peak during mechanical inspiration at different peak airway pressures (Paw). The inspiratory CO_2 peak first appears at a peak Paw of 30 cm H_2O and becomes progressively higher as peak Paw increases.

pling tube and we postulate that the trap consists of two compartments (Fig. 4). In the upper compartment, sampled gas exits the sampling tube and flows into a tube leading to the CO_2 analyzer cell at a rate

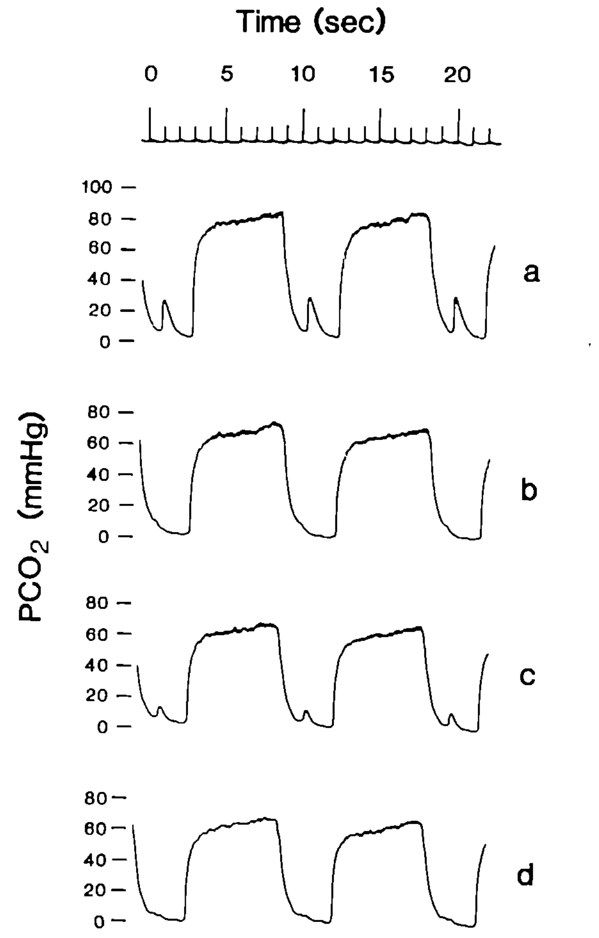

Figure 3. Capnograms recorded experimentally. The endotracheal tube was partially obstructed and peak airway pressure was 50 cm H_2O. Baseline values were obtained (a); then measurements were made with the 30-ml water trap bypassed (b), filled with 10 ml of water (c), and filled with 20 ml of water (d).

of 150 ml/min. A small portion of the gas sample flows into the lower part of the water trap (30 ml/min), and there the concentrations of gases are averaged over several breaths.

At end inspiration (Fig. 4*A*), air in the sampling tube, water trap, and capnograph equilibrates with Paw. The ventilator then initiates exhalation by releasing the pressure (Fig. 4*B*); the compressed air expands and part of the gas in the water trap flows back into the sampling tube. Subsequently, this gas from the water trap, which contains CO_2, is sampled by the capnograph, which displays an artifact because the CO_2 that is measured is temporally unrelated to expired gas. When the 30-ml water trap is filled with air, it is pressurized at a Paw of 50 cm H_2O and expands to about 31.5 ml at atmospheric pressure; this results in 1.5 ml of air flowing from the water trap back into the sampling tube.

The process of gas sampling explains the position

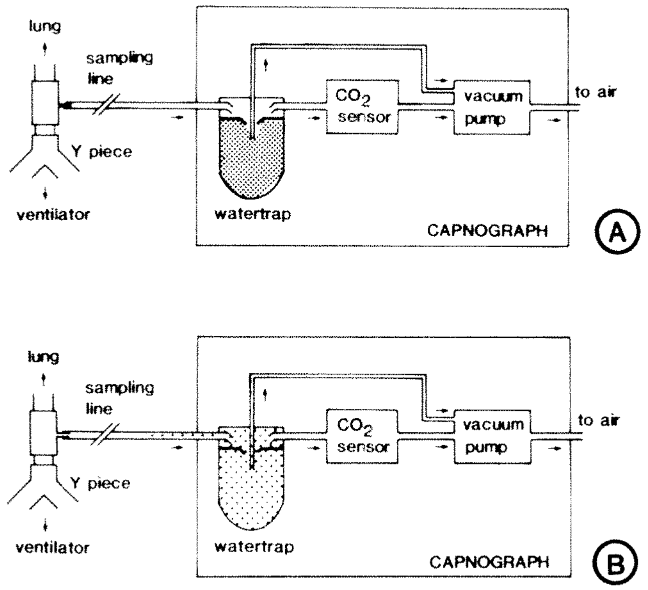

Figure 4. Schema of gas sample route in the capnograph. (**A**) At the end of inspiration the system is pressurized at peak airway pressure (Paw) and filled with fresh gas except for the lower part of the water trap, which holds a gas mixture containing CO_2 (shaded). (**B**) At the beginning of expiration, Paw decreases to baseline. The pressurized gas mixture in the lower part of the water trap expands and some flows back into the sampling tube, the CO_2 content of which is eventually detected by the capnograph.

of the artifact in the capnogram. The sampling time (St) is defined as the time it takes for a gas sample to flow through the sampling tube at a specific sampling rate. The capnograph time (Ct) is defined as the interval of time between the arrival of a gas sample at the water trap and the electrical registration of this gas sample on the recorder. The measurement time (Mt) is the total time of both periods: Mt = St + Ct.

The normal capnogram, which shows P_{CO_2} in respired gases, is delayed by Mt, but the artifact appears after a delay of Ct. The artifact, although originating at the beginning of expiration, appears in the preceding inspiratory phase of the capnogram as a result of the phase difference, St = Mt − Ct. Capnograph time was determined experimentally to be 0.67 ± 0.03 sec. The artifact time (At) was determined to be the time elapsed between the decrease of Paw to baseline and the appearance of the artifact: At = 0.71 ± 0.03 sec. That artifact time approximately equals capnograph time (they do not differ statistically) verifies this explanation.

Recordings made at different respiratory rates (Fig. 5) showed that the water trap-related artifact can appear in both the inspiratory and expiratory phase of the capnogram or can be disguised completely in the expiratory phase by variations in the duration of inspiration with different respiratory rates.

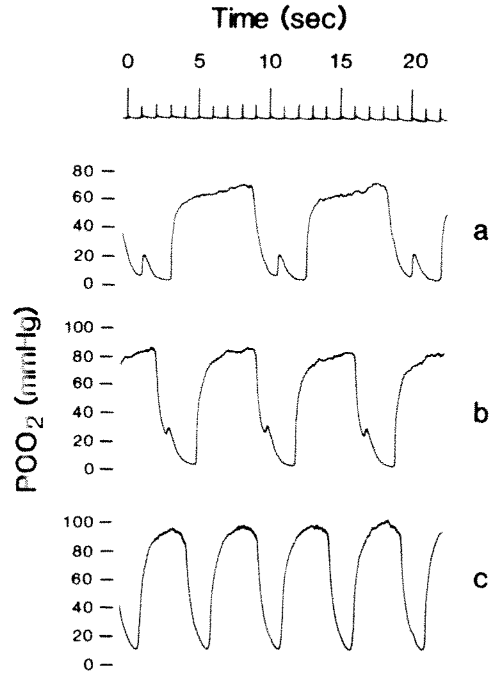

Figure 5. Capnograms recorded experimentally with the endotracheal tube partially obstructed. (**A**) With baseline values at a respiratory rate of 6/min, the CO_2 artifact appears during the capnographic inspiratory phase. (**B**) With a respiratory rate of 8/min, the artifact appears in the capnographic expiratory phase. (**C**) With a respiratory rate of 12/min, the artifact is disguised by the expiratory phase.

The water trap in a capnograph removes moisture from a gas sample before it reaches the CO_2 analyzer cell. The volume of this water trap appears to be critical in generating accurate capnograms at elevated Paw. The artifact disappeared when the water trap volume was reduced from 30 to 10 ml (Fig. 3). We suggest that capnograph manufacturers limit the size of such water traps to prevent capnogram artifacts at elevated Paw or verify that their water trap system does not generate artifacts.

References

1. Smalhout B, Kalenda Z. An atlas of capnography. Zeist, Netherlands: Kerckebosch, 1975.
2. Gravenstein N, Lampotang S, Beneken JEW. Factors influencing capnography in the Bain circuit. J Clin Monit 1985;3:6–10.

Clinical Reports

Prolonged Neuromuscular Paralysis with Vecuronium in a Patient with Polymyositis

Gary Flusche, MD, Julian Unger-Sargon, MB, and Donald H. Lambert, PhD, MD

Certain patients with dermatomyositis show a profound peripheral weakness. In some, this weakness is improved with the administration of anticholinesterase drugs. In 1958, Churchill-Davidson and Richardson investigated ten patients with dermatomyositis (1). They found evidence of a myasthenic response (using decamethonium) in two: in one of these patients a bronchogenic neoplasm was present. These authors caution, therefore, that muscle relaxants be used carefully when anesthetizing patients with dermatomyositis. The present report describes a case of prolonged neuromuscular blockade with the short-acting, nondepolarizing relaxant vecuronium in a patient with polymyositis who subsequently displayed no abnormality of neuromuscular transmission on electromyographic testing.

Case Report

A 73-yr-old white woman with longstanding rheumatoid arthritis and a 10-yr history of polymyositis, peripheral vascular disease, and hypertension required femoral–popliteal thrombectomy. She had undergone two previous lower extremity revascularizaton procedures under regional anesthesia in the preceding three years and had two clinically significant episodes of lower extremity deep vein thrombosis that required treatment with coumadin for 3–6 months during the past two years. The diagnosis of polymyositis was based on clinical presentation, elevated serum creatine phosphokinase levels, and characteristic muscle biopsy. Three years previously she had had a left hemisphere cerebrovascular accident that left her with minimal residual right hand clumsiness. She also had a large but infrequently symptomatic hiatal hernia.

Three weeks before surgery, the patient was admitted because of acute onset of left leg arterial insufficiency and an *Escherichia coli* urinary tract infection. Aminoglycoside therapy was terminated 2 weeks before surgery when her renal function deteriorated. During subsequent therapy she developed pancytopenia. Before the operation, transfusions had restored the hematocrit to 34%, and renal function had returned to baseline (serum BUN concentration 37 mg/dl [12.2 mmol/L] and creatinine concentration 1.8 mg/dl [137 μmol/L]). Daily medications at the time of surgery were 15 mg prednisone, 50 mg mercaptopurine, 150 mg metoprolol, 500 mg methyldopa, and dipyridamole. She had completed antibiotic therapy 3 days before surgery.

Preoperative physical examination showed her to be 160 cm tall, weighing 60 kg, with a blood pressure of 140/80 mm Hg, pulse rate of 60, and respirations 16/min. Neck extension and mouth opening were limited; only lower teeth were present. Lungs were clear. Auscultation of the heart showed a normal S1, an increased S2, and a grade 3/6 systolic ejection murmur at the left sternal border. The electrocardiogram showed sinus rhythm, left atrial enlargement, and borderline left ventricular hypertrophy. Chest radiographs showed a large hiatal hernia, calcification of the mitral annulus and lower vertebral compression fractures. Neuromuscular examination demonstrated 4/5 strength in hip flexion and triceps extension, with other muscle strength 5/5.

Concentrations of serum electrolytes, uric acid, albumin, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, bilirubin, and alkaline phosphatase were normal. There was a slight elevation of

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Received from the Departments of Anesthesia and Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Accepted for publication August 19, 1986.

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the concentration of lactic dehydrogenase. The patient was calm and drowsy 1 hr after intramuscular morphine, 3 mg, scopolamine, 0.2 mg and droperidol, 1.25 mg. Methylprednisolone, 40 mg intramuscularly was also given. Because of rheumatoid arthritis-related limitations of mouth opening and neck extension, awake visualization of the airway was performed using 2 ml of 4% topical lidocaine administered by atomizer plus 2 mg of diazepam IV. Only the tip of the epiglottis could be visualized with the patient awake, but it was felt that the patient could be safely intubated with the addition of muscle relaxants. The patient was then given 75 mg of thiopental and 0.10 mg fentanyl, IV, and was intubated after 8 mg vecuronium (0.13 mg/kg) in anticipation of a 3-hr procedure. This relatively large dose of vecuronium was also chosen to speed the onset of muscle relaxation to facilitate intubation because of the increased risk of aspiration due to the presence of the patient's hiatal hernia. Anesthesia was maintained with oxygen and nitrous oxide 1:1 and enflurane 0.3–1%. During the last hour of the operation, morphine, 3 mg IV, was given (in anticipation of postoperative pain) and enflurane remained at 0.3% until stopped 10 min before attempting neuromuscular blockade reversal. Other intraoperative medications given parenterally, included cefazolin, 1 g, 100 ml of dilute contrast agent for four intraoperative arteriograms, methylprednisolone, 40 mg, heparin, 5000 U, and protamine, 50 mg.

Neuromuscular blockade was monitored with a Ministim® (Professional Industries, Houston, TX), which delivers supramaximal stimuli at 2 Hz or 100 Hz. At 2.5 hr after the sole dose of vecuronium (8 mg), visual observation of thumb adduction after ulnar nerve stimulation for 2 sec at 2 Hz (train-of-four) demonstrated one thumb twitch. Initial neuromuscular reversal was attempted using neostigmine, 4 mg (0.67 mg/kg), and glycopyrrolate, 0.8 mg (0.013 mg/kg), I.V. Fifteen minutes after these drugs had been given and 25 min after the 0.3% enflurane was stopped, the visually observed thumb adduction in response to train-of-four stimulation displayed four thumb twitches but with significant fade. Thirty minutes later, edrophonium, 30 mg, and glycopyrrolate, 0.2 mg, given intravenously eliminated the train-of-four fade, but the tetanic response to 100 Hz stimulation was not sustained. Ventilatory support continued during the reversal attempts and the patient required 9.5 hr of postoperative ventilation to meet clinical criteria for extubation (inspiratory force = −20 cm H_2O, vital capacity = 15 ml/kg.) The reason for the discrepancy between the recovery of the train-of-four response and continued respiratory inadequacy is not clear. The postoperative neurologic examination was the same as it was preoperatively. This operation was the patient's first exposure to neuromuscular blocking agents since developing polymyositis.

Some time after this procedure the patient underwent standard electromyographic (EMG) examination. This neurophysiological examination showed "evidence of loss or block of muscle fibers in the left medial vastus, brachial biceps, deltoid, and triceps muscles. In addition, there was evidence of ongoing denervation with fibrillation and positive sharp waves in the left brachial biceps and left triceps muscle." These findings are compatible with an inflammatory myopathy. In addition, evoked muscle action potentials recorded from the deltoid muscle after supramaximal stimulation of the axillary nerve at 2–5 Hz for 2–3 sec revealed no decrement. Thus, there was no evidence of myasthenia gravis or other defects in neuromuscular transmission.

Discussion

Kunjappan et al. (2) have recently shown that intubating doses of vecuronium (0.15 mg/kg) in patients 17–83 yr block neuromuscular transmission for 39.7 ± 4.34 min (mean ± SEM). Thus, the prolonged paralysis that we report here is greatly in excess of what was anticipated.

Although this patient had a mildly elevated serum creatinine concentration we do not attribute the prolonged neuromuscular blockade to compromised renal function because elimination of vecuronium is not heavily dependent on the kidney. Biliary excretion is considered to be the predominant route of elimination and this patient had normal hepatic function.

Polymyositis and dermatomyositis involve symmetrical, bilateral neck, shoulder, and pelvic muscle weakness in 50% of cases. There may also be weakness of the intercostal and diaphragmatic muscles and muscles necessary for swallowing (3). No clinical evidence of muscle impairment in these areas was noted in our patient before surgery.

Pathologically, polymyositis is characterized by myofibril perivascular inflammatory infiltrates and muscle fiber degeneration. Electromyographic evidence of muscle fiber fibrillation and sharp wave activity is associated with active disease. Nerve conduction velocity is normal but muscle action potentials are decreased in amplitude and duration. The pathological changes of polymyositis are believed to occur distal to the neuromuscular junction, with no alteration in acetylcholine function or degradation, though myasthenic-like syndromes have been reported in patients with polymyositis (1). This patient underwent postoperative EMG testing that confirmed findings consistent with an active inflammatory myopathy, but excluded neuromuscular transmission abnormalities. Both prejunctional and postjunctional sites of action have been proposed for vecuronium (4), but neither of these sites should be influenced by the pathology of polymyositis.

The cause of this patient's prolonged response to vecuronium is obscure. Disorders that impair the structure and function of the nerve and muscle fibers might be expected to damage the adjacent neuromuscular junction. The functional reserve of the neuromuscular junction is such that subclinical alterations may not be revealed by physiologic studies. Thus, widespread subclinical alterations in neuromuscular function may pass unobserved in a disorder such as polymyositis unless the patient is exposed to muscle relaxants (5). The undue sensitivity to vecuronium in this patient may indicate a subclinical defect of neuromuscular transmission and may be similar to that seen with Duchenne muscular dystrophy (5) and neurofibromatosis (6). Because we are not aware of other reports of prolonged neuromuscular blockade with nondepolarizing muscle relaxants in polymyositis, we suspect that this is not a common problem in these patients.

Alternatively, the prolonged response we encountered in this patient may simply be a manifestation of the wide variation in response to neuromuscular blockade (with *d*-tubocurarine) reported by Katz (7). However, it is not known if similar variations in response occur with vecuronium. Finally, none of the medications taken by the patient preoperatively or given to the patient intraoperatively are known to prolong nondepolarizing muscle relaxants. Whether or not polypharmacy together with mild renal impairment could produce the prolonged neuromuscular blockade reported here is another, albeit speculative, alternative.

In summary, we report a case of prolonged neuromuscular blockade with vecuronium in a patient with polymyositis in whom no abnormality of neuromuscular transmission was found on subsequent electromyographic analysis. This is probably an uncommon manifestation of this disease. Additional studies of patients with polymyositis who receive nondepolarizing neuromuscular blocking agents are necessary to quantitate the magnitude of what may be a subclinical defect in neuromuscular transmission.

References

1. Wylie WD, Churchill-Davidson HC. A practice of Anaesthesia. 5th ed. Philadelphia: WB Saunders, 1984:744.
2. Kunjappan VE, Brown EM, Alexander GD. Rapid sequence induction using vecuronium. Anesth Analg 1986;65:503–6.
3. Katz J, Benumof J, Kadis LB. Anesthesia and Uncommon Diseases. 2nd ed. Philadelphia: WB Saunders, 1981:523–4.
4. Bowman WC. Prejunctional and postjunctional cholinoceptors at the neuromuscular junction. Anesth Analg 1980;59:935–43.
5. Brown JC, Charlton JE. Study of sensitivity to curare in certain neurological disorders using a regional technique. J Neurol Neurosurg Psychiatr 1975;38:34–45.
6. Baraka A. Myasthenic response to muscle relaxants in Von Recklinghausen's disease. Br J Anaesth 1974;46:701–3.
7. Katz RL. Neuromuscular effects of *d*-tubocurarine, edrophonium and neostigmine in man. Anesthesiology 1967;28:327–36.

ANESTH ANALG
1987;66:191–2

Effect of Cimetidine on Duration of Action of Succinylcholine

J. Reddy Kambam, MD, Richard Dymond, MD, and Michael Krestow, MD

Administration of cimetidine, an H_2-receptor antagonist, is associated with a direct inhibition of liver microsomal enzymes and a decrease in liver blood flow resulting in a variety of clinically significant drug interactions (1,2). Cimetidine is one of the more frequently prescribed drugs in the United States and a large number of these patients who are taking cimetidine are coming to the operating room today. The effects of cimetidine on the action of muscle relaxants have not been reported. The purpose of the present study is to investigate the effects of cimetidine on the onset and duration of action of succinylcholine.

Methods

Twenty ASA Class 1 consenting patients between 20 and 40 years of age were included in this study. The patients were divided into two groups (n = 10 each). Group 1 received 300 mg cimetidine orally at bed time and 300 mg orally 2 hr before induction of general anesthesia. Group 2 patients acted as control and did not receive cimetidine. All patients received meperidine, 1 mg/kg intramuscularly, and phenergan, 0.5 mg/kg intramuscularly, as preoperative medications 2 hr before induction of anesthesia with 6 mg/kg of IV thiopental. The median nerve at the wrist was stimulated supramaximally and the integrated electromyographic (IEMG) response from the thenar muscle was monitored continuously with the Monash Neuro Muscular Block Monitor (Electro Med, Australia). The value of the IEMG at anytime is displayed digitally as a percentage of its value before the induction of muscle relaxation. Succinylcholine, 1.5 mg/kg IV, was used in each patient and tracheal intubation performed when 95% depression of twitch height was present. Anesthesia was maintained with 60% N_2O in 39% O_2 and 1% halothane. Ventilation was controlled using a tidal volume of 12 ml/kg at a rate of 10/min. The time taken for spontaneous recovery from the time succinylcholine was administered to 50% of control twitch height was noted in all patients. Data were analyzed for statistical significance by means of Student's *t*-test (two-tailed).

Results

Results are shown in Table 1. Onset of action of succinylcholine was not related to cimetidine, but duration of action was significantly prolonged in patients given cimetidine. In one of the patients given cimetidine the time for initial recovery of twitch after succinylcholine administration was 45 min. Twitch height returned to 50% of control 57 min after the administration of succinylcholine. The plasma pseudocholinesterase level and fluoride number in this patient (measured 24 hr postoperatively by PCHE pack and Du Pont aca discrete clinical analyzer in our hospital laboratory) were in the normal range.

Discussion

Cimetidine is frequently used by anesthesiologists for controlling the pH and volume of gastric contents. Cimetidine interacts with the pharmacokinetics of a variety of drugs including lidocaine, narcotics, and benzodiazepines (3–5). Cimetidine is also used along with H_1-receptor antagonists for prevention of histamine-related side effects caused by narcotics and muscle relaxants (6,7).

We found in the present study that the duration of action of succinylcholine is 2 to 2.5 times longer in patients given cimetidine preoperatively than it is in patients not given cimetidine, a statistically significant difference. We also conclude that, in an occasional patient receiving cimetidine, it takes several minutes to an hour before recovery from muscle relaxation produced by succinylcholine is complete, and this too is clinically significant. The mechanisms for the prolongation of succinylcholine action caused by cimetidine need to be investigated.

Received from the King Fahad Hospital, Riyadh, Saudi Arabia. Accepted August 6, 1986.

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Table 1. Effect of Cimetidine on the Action of Succinylcholine

	Control group		Cimetidine group	
Subjects	Onset of[a] action (sec)	Duration[b] of action (min)	Onset of[a] action (sec)	Duration[b] of action (min)
1	36	8	37	18
2	70	11	33	10
3	35	11	40	57
4	38	7	83	21
5	35	8	33	20
6	40	4	34	11
7	38	8	85	20
8	70	10	32	15
9	68	7	90	18
10	70	12	33	13
Mean ± SEM	50 ± 5.0	8.6 ± 0.76	50 ± 7.5	20.3 ± 4.25

[a] No significant difference between the two groups (onset of action = time from injection to 95% twitch depression).

[b] Significant difference between the two groups ($P < 0.05$), Student's t-test, two-tailed value (duration of action = time from injection to 50% twitch recovery).

References

1. Puurunen J, Sotaniemi E, Pelkonen O. Effect of cimetidine on microsomal drug metabolism in man. Eur J Clin Pharmacol 1980;18:185–7.
2. Freely J, Wilkinson GR, Wood AJJ. Reduction of liver blood flow and propranolol metabolism by cimetidine. N Engl J Med 1981;304:692–5.
3. Jackson JE, Bentley JB, Glass SJ, Fukui T, Gandolfi AJ, Plachetka JR. Effect of histamine-$_2$ receptor blockade on lidocaine kinetics. Clin Pharmacol Ther 1985;37:544–8.
4. Sorkin EM, Ogawa GS. Cimetidine potentiation of narcotic action. Drug Intell Clin Pharm 1983;17:60–1.
5. Greenblatt DJ, Abernathy DR, Morse DS, Harmatz JS, Shader RI. Clinical importance of the interaction of diazepam and cimetidine. N Engl J Med 1984;310(21):1639–43.
6. Philbin DM, Moss J, Akins CW, Rosow CE, Kono K, Schneider RC, Verlee TR, Savarese JJ. The use of H1 and H2 histamine antagonists with morphine anesthesia: a double blind study. Anesthesiology 1981;55:292–6.
7. Scott RPF, Savarese JJ, Basta SJ, et al. Atracurium: clinical strategies for preventing histamine release and attenuating the haemodynamic response. Br J Anaesth 1985;57:550–3.

ANESTH ANALG
1987;66:193–5

Status Asthmaticus Treated with Isoflurane and Enflurane

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Severe bronchospasm that is refractory to aggressive medical therapy and that requires tracheal intubation and mechanical ventilation is rare, occurring in only about 2% of patients hospitalized for asthma (1). Indeed, tracheal intubation may even worsen bronchospasm, and mechanical ventilation in status asthmaticus is associated with substantial morbidity and mortality (1). Heavy sedation and paralysis with pancuronium bromide may facilitate mechanical ventilation (2), but have no direct bronchodilatory effects. Inhalational anesthetics have been used as bronchodilators for many years. In particular, halothane has been recommended for asthmatics refractory to maximal medical therapy (3), but its use has been limited by the risk of life-threatening arrhythmias (4). There are, however, other inhalational anesthetics with bronchodilatory effects that are less arrhythmogenic (5).

We report three patients with status asthmaticus refractory to maximal medical therapy who continued to deteriorate after intubation and paralysis but responded dramatically to the use of isoflurane and enflurane.

Case Reports

Patient 1

A 27-yr-old woman was admitted in status asthmaticus. Treatment with oxygen, nebulized isoetharine, subcutaneous epinephrine, and intravenous aminophylline and hydrocortisone was unsuccessful. She became increasingly short of breath and lethargic. She was intubated, connected to a Bear 2 volume ventilator (F_{IO_2} 0.50), sedated with diazepam and fentanyl, and paralyzed with pancuronium bromide. Her condition continued to deteriorate rapidly, as evidenced by air trapping and incomplete expiratory phase, the need for peak inspiratory pressures of greater than 60 cm H_2O, and arterial blood gas analysis showed a pH of 7.16, a P_{CO_2} of 69 mm Hg, and a P_{O_2} of 146 mm Hg (F_{IO_2} 0.50). Ventilator settings for tidal volume, inspiratory flow, and rate (range, 8–15/min) were changed over the next half hour without improvement.

Isoflurane was then administered in oxygen via an anesthesia machine with manual ventilation at rates of 6–16/min, increasing with increased air movement, and then switched to mechanical ventilation as air movement became progressively easier. Inhaled isoflurane concentration varied between 0.25% and 2% in the attempt to provide bronchodilation while also maintaining a systolic blood pressure above 100 mm Hg. Within 15 min bronchodilation occurred as evidenced by improved air movement, a decrease in peak inspiratory pressure to 45 cm H_2O, decreased wheezing, and improvement in arterial blood gas values to pH 7.23, P_{CO_2} 56 mm Hg, and P_{O_2} 381 mm Hg. (Peak airway pressures were determined by briefly reconnecting the patient to the Bear 2 ventilator and delivering a breath at the same settings used before anesthesia.) Thirty minutes later peak inspiratory pressure was 40 cm H_2O and arterial blood gas analysis revealed a pH of 7.27, a P_{CO_2} of 48 mm Hg, and a P_{O_2} of 340 mm Hg. Ninety minutes later she had no further wheezing, peak pressure was 30 cm H_2O, and arterial blood gas analysis showed a pH of 7.39 with a P_{CO_2} of 37.9 mm Hg. Isoflurane was continued for 1 hr. She was extubated breathing comfortably and spontaneously 4 hr later.

Patient 2

A 57-yr-old woman presented to the emergency room with wheezing. Treatment with oxygen by mask, nebulized metaproterenol sulfate, and intravenous aminophylline, hydrocortisone, and penicillin was un-

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Received from the Departments of Medicine and Anesthesiology, and the Multidisciplinary Intensive Care Unit, Michael Reese Hospital and Medical Center, University of Chicago, Pritzker School of Medicine, Chicago, Illinois. Accepted for publication August 19, 1986.

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successful. Arterial blood gas analysis showed a pH of 7.28, a P_{CO_2} of 43 mm Hg. and a P_{O_2} of 70 mm Hg. She became increasingly fatigued and lethargic. She was then intubated, connected to a Bear 2 volume ventilator, sedated with fentanyl and paralyzed with atracurium. Arterial blood gas values deteriorated to pH 7.16, P_{CO_2} 57 mm Hg, P_{O_2} 127 mm Hg, and peak pressures were greater than 50 cm H_2O. Adjustment of ventilator settings had little effect on ventilation.

She was started on enflurane with oxygen via an anesthesia machine with manual ventilation and then mechanical ventilation, titrating the concentration of enflurane to maintain a systolic blood pressure above 90 mm Hg. Within 15 min wheezing had disappeared, peak inspiratory pressure had decreased to 30 cm H_2O, and arterial blood gas values were pH 7.25, P_{CO_2} 43 mm Hg, and P_{O_2} 94 mm Hg. Enflurane was discontinued after 2 hr. Although mild wheezing returned and peak pressures increased to 40 cm H_2O, arterial blood gases changed only slightly. Paralysis was continued with pancuronium bromide, and sedation with fentanyl and diazepam. She was mechanically ventilated for another 14 hr at which time she was extubated. Her subsequent hospital course was uneventful.

Patient 3

A 53-yr-old woman came to the emergency room with wheezing. Therapy included aminophylline, nebulized metaproterenol sulfate, and hydrocortisone sodium succinate. There was no improvement over 36 hr, at the end of which time values from arterial blood gas analysis were pH 7.32, P_{CO_2} 51 mm Hg, and P_{O_2} 127 mm Hg. She was then intubated, paralyzed with pancuronium bromide because of peak inspiratory pressures greater than 60 cm H_2O, and sedated with fentanyl. Arterial blood gas values stabilized at pH 7.41 and P_{CO_2} 45 with peak pressures of 40 cm H_2O. Over the next 12 hr pancuronium and fentanyl were discontinued. Six hours later peak inspiratory pressures increased to 60–70 cm H_2O and arterial P_{CO_2} to 67 mm Hg with a pH of 7.24.

Enflurane was administered via an anesthesia machine with manual and then mechanical ventilation titrating to a systolic blood pressure of 100 mm Hg. Marked resistance to ventilation decreased within 30 min, with peak inspiratory pressure and end inspiratory pressure of 38 and 32 cm H_2O, respectively. Arterial blood gas values improved to pH 7.33 and P_{CO_2} 53 mm Hg. Wheezing decreased but there was no further improvement over the next hour as measured by arterial blood gas analysis, and peak inspiratory and end-inspiratory pressures. Isoflurane was then started at 1% followed by concentrations associated with systolic blood pressures above 100 mm Hg. Fifteen minutes later there was no wheezing, peak inspiratory and end inspiratory pressures were 27 and 24 cm H_2O, respectively, and arterial blood gas values of pH 7.45 mm Hg and P_{CO_2} 42 mm Hg. Isoflurane was discontinued after 3 hr and the patient was supported by mechanical ventilation for another 12 hr before being successfully extubated.

Discussion

Asthma is a relatively common disease in which most patients, including those in status asthmaticus, usually respond to conventional therapy with oxygen, epinephrine, aminophylline, inhalational β-adrenergic agonists, and the early use of corticosteroids. A minority of patients do not respond and require tracheal intubation and mechanical ventilation. This group comprised 2% of 811 patients reported by Scoggin et al. with a mortality of 38% among the intubated patients (1). The mortality rate in other series of patients requiring mechanical ventilation, surveyed by Scoggin et al., ranged from 0% to 38%. Heavy sedation and paralysis in intubated patients facilitate mechanical ventilation by preventing bucking, but have no direct bronchodilatory effect (2). Additional pharmacologic therapy would be desirable in these patients and possible benefits of inhalation anesthetics have been considered.

As a bronchodilator, enflurane is as effective as halothane in the ascaris-antigen dog model of asthma (6) and is able to block hypocapnic bronchoconstriction in the canine lung (7). Isoflurane has also been shown to be as effective as halothane in attenuating allergic bronchoconstriction in an animal model (8). Neither isoflurane nor enflurane has been associated with arrhythmias in conjunction with epinephrine and aminophylline, as halothane has (4,5,9). We therefore used these bronchodilating agents in our patients when they deteriorated after intubation and paralysis. In patient 2 the use of atracurium, which can cause histamine release, may have contributed to the deterioration of the patient's ventilatory status. Nonetheless, the response to enflurane in this patient indicates its value in refractory bronchospasm. Our third patient showed improvement from a life-threatening situation with enflurane, but the response was not as complete as in our first two patients. We therefore tried isoflurane with resulting dramatic improvement.

Echeverria et al. reported a patient with status asthmaticus refractory to conventional therapy and mechanical ventilation who failed to respond to enflurane but responded well to halothane (10). Robertson et al. have similarly reported two patients who failed to respond to halothane but had a prompt bronchodilator response to diethyl ether (11).

Our case reports as well as those of others suggest there is variability in patient response to inhalational anesthetics during status asthmaticus. Failure or incomplete response to one agent does not preclude a favorable response to another. There have not been enough studies to determine if any agent is clearly superior. Given the arrhythmogenic potential of halothane and the risk of explosion and flammability with ether we recommend using isoflurane or enflurane first and switching to the others should the need arise. Isoflurane, which has little effect on cardiac output, may be the preferred agent in patients with limited cardiac reserve. Further study is needed in this area to determine the optimal agent.

In summary, we describe three patients with status asthmaticus refractory to maximal medical therapy and mechanical ventilation who, when treated with isoflurane and enflurane, had rapid bronchodilation. Isoflurane and enflurane are potent bronchodilators; moreover, in comparison to halothane they are not arrhythmogenic and may be the agents of choice in selected cases of refractory status asthmaticus.

The authors wish to thank Ms. Sherry Alonzo for her secretarial assistance in the preparation of this manuscript and Verna Baughman, MD, for editorial assistance.

References

1. Scoggin CH, Sahn SA, Petty TL. Status asthmaticus: a nine year experience. JAMA 1977;238:1158–62.
2. Levin N, Dillon JB. Status asthmaticus and pancuronium bromide. JAMA 1972;222:1265–8.
3. Schwartz S. Treatment of status asthmaticus with halothane. JAMA 1984;251:2688–9.
4. Roizen MF, Stevens WC. Multiform ventricular tachycardia due to the interaction of aminophylline and halothane. Anesth Analg 1978;57:738–41.
5. Johnston RR, Eger EI, Wilson C. A comparative interaction of epinephrine with enflurane, isoflurane, and halothane in man. Anesth Analg 1976;55:709–12.
6. Hirshman CA, Bergman NA. Halothane and enflurane protect against bronchospasm in an asthma dog model. Anesth Analg 1978;57:629–33.
7. Coon RL, Kampine JP. Hypocapnic bronchoconstriction and inhalation anesthetics. Anesthesiology 1975;43:635–41.
8. Hirshman CA, Edelstein G, Peetz S, Wayne R, Downes H. Mechanism of action of inhalational anesthesia on airways. Anesthesiology 1982;56:107–11.
9. Stirt JA, Berger JM, Sullivan SF. Lack of arrhythmogenicity of isoflurane following administration of aminophylline in dogs. Anesth Analg 1983;62:568–71.
10. Echeverria M, Gelb AW, Wexler HR, et al. Enflurane and halothane in status asthmaticus. Chest 1986;89:152–4.
11. Robertson CE, Steedman D, Sinclair CJ, et al. Use of ether in life-threatening acute severe asthma. Lancet 1985;i:187–8.

Letters to the Editor

A Case of Difficult Neonatal Ventilation

To the Editor:

We would like to bring to the attention of others an unusual problem that we encountered recently. A 15-yr-old patient, 34-weeks pregnant, was scheduled for elective cesarean section because of severe intrauterine fetal growth retardation secondary to severe uncorrected maternal coarctation of the aorta. After careful evaluation we decided to proceed with a general anesthetic using fentanyl (25 μg/kg), in order to minimize maternal cardiovascular changes. It was predicted that the newborn would exhibit respiratory depression, and adequate preparations for its treatment were made.

The 2400-g baby was, as anticipated, floppy and without respiratory effort when delivered, but it appeared otherwise normally developed. The baby was intubated without difficulty. However, the chest did not expand adequately with positive pressure ventilation. Air entry was poor bilaterally, and high inspiratory pressures were required for any entry to occur. Among the differential diagnoses entertained at this moment were meconium aspiration, diaphragmatic hernia, pneumothorax, and tracheal or bronchial stenosis (1). The diagnosis was made when the IV administration of 0.02 mg of naloxone resulted in a sudden and drastic reduction of the pressure required to ventilate the neonate. After further naloxone and a short period of ventilation, spontaneous respirations were established, and the baby was extubated without further problems.

When the anesthetic technique was selected, we anticipated that the baby was going to be floppy and with respiratory depression. The fentanyl-induced chest wall rigidity encountered was not predicted. Though previously reported in adults (2), the occurrence of fentanyl-induced chest wall rigidity with immediate relief after naloxone has not, to the best of our knowledge, been previously reported in neonates.

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References

1. Schaffer's Diseases of the Newborn, 5th edition. Philadelphia: WB Saunders Co, 1984.
2. Christian CM, Waller JL, Moldenhauer CC. Postoperative rigidity following fentanyl anesthesia. Anesthesiology 1983;58:275–7.

Esophageal Activity and Light Anesthesia

To the Editor:

Dr. Meyer is to be congratulated on his clinical acumen in observing changes in the quality of heart and breath sounds, accompanied by "swallowing" noises, during lightening anesthesia (1).

The human esophagus is exceptional in that the musculature of its lower half is nonstriated and thus unaffected by skeletal muscle relaxants; the usual experimental analogue of the human esophagus is found in the American opossum. During lightening anesthesia in humans one can observe a progressive increase in lower esophageal contractility (LEC). These contractions have typical amplitudes of 40–50 mm Hg, but can exceed 100 mm Hg and have a duration of up to 10 sec (Fig. 1). Physiologically they represent stress-induced nonpropulsive tertiary contractions arising from increasing activity in the esophageal motility center (vagal motor nuclei and adjacent reticular formation) in the brain stem mediated via the vagus nerve (2,3).

Suppression of LEC can be achieved by increasing the depth of anesthesia with either inhalational or intravenous agents. LEC can be detected by auscultatory muffling as Dr. Meyer describes but may also be apparent as a rustling of the cuff of the esophageal stethoscope; presumably the compression of the esophageal cuff against the main body of the stethoscope creates noise and the compressed cuff transmits sound poorly.

LEC is not directly affected by muscle relaxants and can certainly be recorded during total skeletal muscle paralysis. The only exception to this rule relates to curare—its ganglion blocking side effect may transiently interfere with recordings of LEC. If the esophageal stethoscope is positioned in the upper esophagus the sign will disappear with full muscle paralysis.

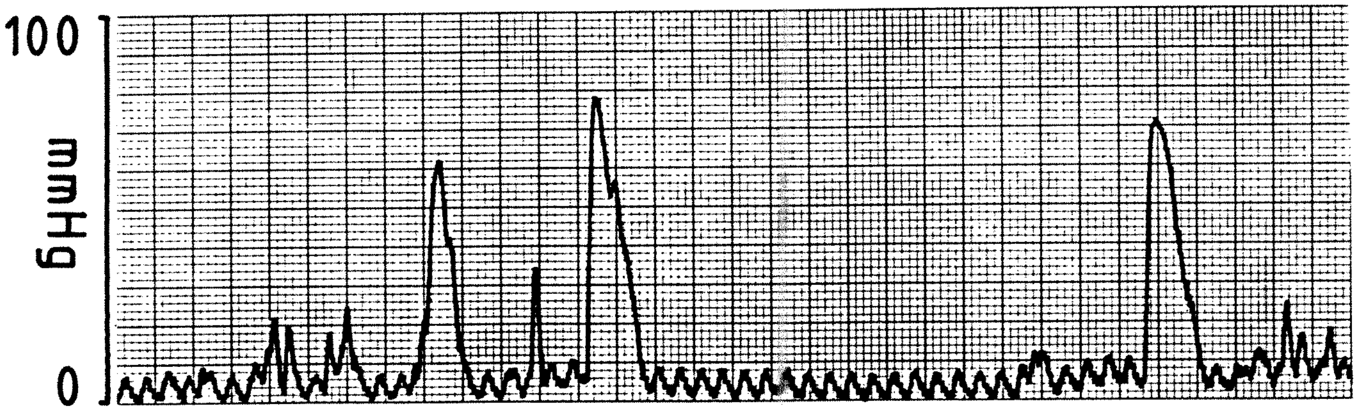

Figure 1. Progressive increase in lower esophageal contractility seen during lightening anesthesia.

Monitoring LEC does provide the anesthesiologist with a useful additional guide to the adequacy of anesthesia (4).

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References

1. Meyer RM. Esophageal stethoscopes can reveal light anesthesia. Anesth Analg 1986;65:319.
2. Stacher G, Schimierer G, Landgraf M. Tertiary oesophageal contractions evoked by acoustical stimuli. Gastroenterology 1979;77:49–54.
3. Rubin J, Nagler, Spiro HM, Pilot ML. Measuring the effect of emotion on esophageal motility. Psychosom Med 1962;24:170–6.
4. Evans JM, Davies WL, Wise CC. Lower oesophageal contractility: a new monitor of anaesthesia. Lancet 1984;i:1151–4.

Prolonged Unilateral Mydriasis after Nasal Septal Reconstruction

To the Editor:

Prolonged unilateral mydriasis after anesthesia may denote a severe neurologic insult. We have recently encountered an unusual case of persistent, postoperative unilateral mydriasis (anisocoria) in which the mechanism did not involve tissue injury.

A healthy 61-yr-old male received enflurane and N_2O anesthesia for nasal septal reconstruction. Intraoperatively, the patient's eyes were closed and covered with gauze sponges that were taped in place, and the ocular padding was covered by a dressing that encircled the head. The supine patient was placed slightly head-down, and the neck was hyperextended. The surgeon injected 5 ml of lidocaine 1% with 10 μg/ml epinephrine into the nasal septum, followed 5 min later by injection of an additional 2 ml of the same solution. During the procedure, the nasal mucosa was also swabbed with felt pledgetts soaked in a 5% solution of cocaine. Vital signs remained stable, and surgery proceeded uneventfully for 40 min. At the conclusion of the anesthetic, the patient was alert, comfortable, and responded to commands appropriately; however, the right pupil was noted to be widely dilated and unresponsive to light. The patient also complained of blurred vision in the right eye. Complete neurologic exam revealed no other deficits; specifically, the extraocular muscles of the right eye functioned normally. The opinion of the consulting ophthalmologist was that the physical findings suggested a drug induced mydriasis, and we decided to simply observe the patient. Eight hours after admission to the recovery room, the patient's right pupil began responding to light, and 18 hr after surgery, the ocular and neurologic examinations were normal.

Drug-induced mydriasis may result from intravascular or topical applications of local anesthetics, catecholamines, or catecholamine-releasing drugs. Previous reports of unilateral mydriasis have implicated the spread of local anesthetics through the inferior orbital fissure after block of the second division of the trigeminal nerve (1), as well as retrograde passage of local anesthetic from the superior alveolar artery to the ophthalmic artery (2), both during tooth extractions. We believe that neither of these mechanisms is applicable to the case at hand because the only injection of local anesthetic in our patient was into the nasal septum, well away from major arteries and the inferior orbital fissure. Due to the manner in which our patient's eyes were protected, it is possible that the unilateral mydriasis resulted from retrograde passage of cocaine (from soaked pledgettes) down the nasolacrimal duct to the eye.

The nasolacrimal duct normally functions to drain tears from the surface of the eye (via the puncta and lacrimal sac) to the nose. It is approximately 1.6 cm in length and contains numerous "valves" (3). The valves are folds of vessel-rich mucous membranes that have little if any valvular function, as fluids and air can be forced up the duct to come out at the puncta (3,4). Placing a patient in the supine position with the neck hyperextended—as was true of our patient—would result in a near vertical path from the inferior nasal

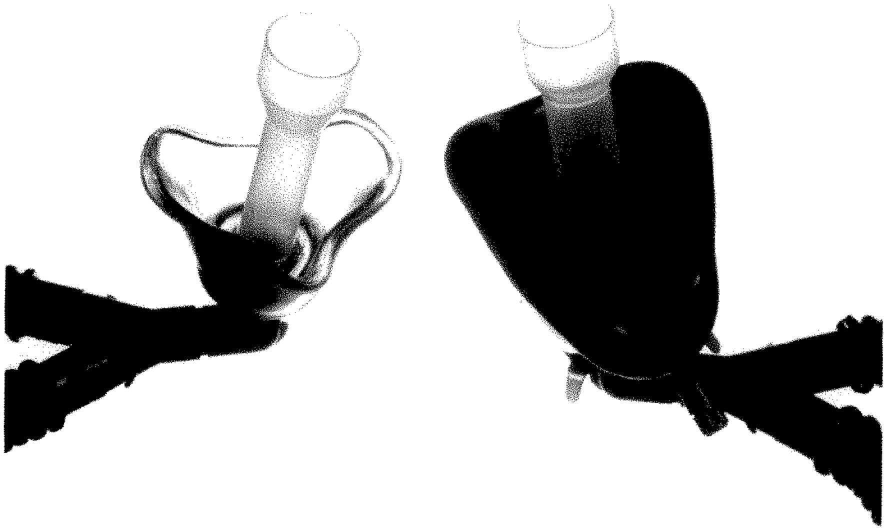

Figure 1. Pediatric circuit occluded by 6-cc syringe container and adult circuit occluded by 12-cc syringe container.

meatus to the eye. Thus it is possible in our patient that cocaine could have passively drained retrograde from the inferior nasal meatus to the eye, resulting in unilateral mydriasis. This passage of local anesthetic could have been facilitated by the ability of cocaine to shrink mucous membranes by its vasoconstrictive effects.

In summary, we report an unusual case of prolonged unilateral mydriasis after nasal septal reconstruction in which the mechanism may have involved the retrograde passage of cocaine to the eye via the nasolacrimal duct.

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References

1. Holmgreen WC, Baddour HM, Tilson HB. Unilateral mydriasis during general anesthesia. J Oral Surg 1979;37:740–2.
2. Hyam SW. Oculomotor palsy following dental anesthesia. Arch Ophthalmol 1976;94:1281–2.
3. Hollinshead WH. Anatomy for surgeons: the head and neck. Philadelphia: Harper and Row, 1982:104–6.
4. Wolff E. The ocular appendages. In: Eugene Wolff's anatomy of the eye and orbit. Philadelphia: W. B. Saunders, 1976:230–2.

A Simple Way to Limit Anesthetic Pollution during Anesthetic Induction

To the Editor:

During anesthetic induction there can be a significant amount of anesthetic gas pollution in the operating room during the period when an anesthetic mask is removed from the patient and endotracheal intubation is accomplished. By using the technique described below, this pollution is minimized. A secondary benefit is that the operating room staff has increased awareness that the anesthesiologist is taking as many precautions as possible to limit environmental hazards.

The hard plastic containers from the needleless Monoject 6-cc and 12-cc syringes (Sherwood Medical, St. Louis, MO 63103) nicely occlude the anesthetic circuit using the pediatric (Rendell-Baker-Soucek, Ohio Medical Products, Madison WI 53701) and adult (Puritan anti-static, Puritan-Bennett Corp., Kansas City, MO 64106) masks available in our operating room (Fig. 1). During laryngoscopy the induction concentration of anesthetic gasses continue to flow with the circuit-mask unit occluded by the syringe container plug allowing the gasses to escape into the scavenge circuit. After intubation the syringe container plug is removed and the circuit is reconnected to the endotracheal tube.

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Difficult Airway?

To the Editor:

Recently I had an experience in the operating room that I would like to share with others. I had a healthy 28-yr old male patient, ASA I, for facial scar revision and reconstruction of the nose. The patient had a history of facial burns six months prior to this procedure. He could open his mouth only 1.5–2 cm because of scar tissue on his face involving both angles of the mouth. In view of this, I decided during my preoperative visit that an awake tracheal intubation using a fiberoptic laryngoscope was indicated. The necessity of this procedure was explained to the patient and he was agreeable to it.

The patient was taken to the operating room the next morning with adequate sedation and preparation for awake oral intubation. In the operating room the surgeon suggested that he could increase the opening of the mouth by cutting the scar after local infiltration of lidocaine. I agreed with this suggestion. This simple step facilitated proceeding with induction of general anesthesia and subsequent intubation, with the patient asleep. Awake intubation had been avoided, and the procedure was uneventful.

The above incidence points out how easy it is to let tunnel vision prevent us from thinking of simpler alternatives in anesthesia.

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Does Silent Aspiration during Endotracheal Anesthesia Cause Pulmonary Aspiration Syndrome?

To the Editor:

I read with interest the study by Petring et al. of silent aspiration due to leaks around cuff of endotracheal tube (1). In their discussion, the authors indicate that severe lung damage is a complication of silent aspiration during endotracheal anesthesia. So-called silent aspiration during anesthesia with or without endotracheal intubation has long been recognized in practice. My search of the literature (Table 1), however, failed to produce evidence of pulmonary complications due to silent aspiration during endotracheal anesthesia. Material that is silently aspirated during general anesthesia could consist of one or more of a mixture of saliva, regurgitated gastric contents, lubricant applied to the endotracheal tube, nasal secretions, secretions from sinuses, tracheal secretions, and even blood associated with trauma during laryngoscopy and intubation. This liquid, laryngotracheal residue, will accumulate above the cuff of endotracheal tube and above the larynx before aspiration occurs. The characteristics of this laryngotracheal residue including pH, viscosity, and volume need to be quantitated, but after my review of the literature I do not believe that the pH and the quantity of aspirate meet the widely cited risk factors of a pH below 2.5 and a volume above 25 ml. Therefore it appears unlikely that pulmonary aspiration syndrome results from silent aspiration during endotracheal anesthesia.

Table 1. Incidence of Silent Aspiration During Anesthesia

Authors	Number of cases	Incidence of aspiration (%)	Pulmonary complications
Culver et al. (2)	300	16.3	None
Berson and Adriani (3)	926	7	None
Lincoln (4)	50	0	None
Marshall and Gordon (5)	219	0.5	None
Gardner and Pryer (6)	109	4	None
Blitt et al. (7)	900	0.6	None
Turndorf et al. (8)	152	0	None

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References

1. Petring OU, Adelhoj B, Jenson BH, Pedersen NO, Lomholt N. Prevention of silent aspiration due to leaks around cuffs endotracheal tubes. Anesth Analg 1986;65:777–80.
2. Culver GA, Makel HP, Beecher HK. Frequency of aspiration of gastric contents by the lungs during anesthesia and surgery. Ann Surg 1951;133: 289–92.
3. Berson W, Adriani J. Silent regurgitation and aspiration during anesthesia. Anesthesiology 1954;15:644–9.
4. Lincoln MW. Aspiration of gastric content under anesthesia. Calif Med 1957;87:403–7.
5. Marshall BM, Gordon RA. Vomiting, regurgitation and aspiration in anaesthesia. Can Anaesth Soc J 5:274–81.
6. Gardner AMN, Pryer DL. Historical and experimental study of aspiration of gastric and oesphageal contents into the lungs in anaesthesia. Br J Anaesth 1966;38:370–9.
7. Blitt CD, Gutman HL, Cohen DD. Silent regurgitation and aspiration during anesthesia. Anesth Analg 1970;49:707–13.
8. Turndorf H, Rodis ID, Clerk TS. Silent regurgitation during anesthesia. Anesth Analg 1974;53:700–3.

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Book Reviews

Extracorporeal Shock Wave Lithotripsy for Renal Stone Disease

Joachim S. Gravenstein and Klaus Peter, eds. Boston: Butterworths, 1986, 158 pp, $19.95.

In 1980 the first patient to have a renal stone successfully pulverized by the energy in shock waves generated outside of his body and brought to focus on a concretion within the renal collecting system was treated at the University of Munich. The process has become known as extracorporeal shock wave lithotripsy (ESWL). The apparatus was developed by Dornier System GmbH of the Federal Republic of Germany.

This volume is the result of a conference held in January 1985 attended by physicians from the University of Florida and the University of Munich and by engineers from Dornier. What has been recorded in this volume is ". . . an initial overview of the theory and application of this new technique, which carries such promise for better patient care." Although the text is typeset, the book is obviously a collection of papers presented at the symposium, with the result that the style is what would be expected to be found in speakers' notes.

There are several chapters devoted to descriptions of physical and engineering considerations necessary to produce and focus shock waves. In interesting early chapters, the reader is made aware that these events occur within the span of a few hundred microseconds and that a great deal more energy than physicians are accustomed to using is required to produce the therapeutic shock waves.

A brief section describes the electrical safety of the machine in terms of the manner in which the current producing the electrical discharge leading to the production of the shock wave is conducted through the water bath surrounding the patient, and how small and transient the currents are that actually reach the patient. Anesthesiologists, who are ordinarily concerned with the hazards of microampere currents leading to ventricular fibrillation, will find that this discussion leaves many unanswered questions concerning the ultimate safety of the lithotriptor because of the large amount of power available from the power mains to the apparatus. A later chapter discusses cardiovascular changes that occur with immersion in patients monitored with central venous or pulmonary arterial lines. This raises a second, unanswered question concerning the potential for problems with leakage currents and suggests a future examination of the interaction of currents which might develop with various failure modes of the lithotriptor and/or monitoring apparatus.

The chapters dealing with specific anesthesia techniques for patients undergoing ESWL indicate that the German experience has favored peridural anesthesia. The group from the United States proposes that high frequency jet ventilation might be used as a way to minimize the movement of the stone and, hence, effect the delivery of more energy to the stone being treated than would occur with movement of the kidney as a consequence of tidal ventilation with either peridural or conventional general anesthesia. Again, clarification of this question must await studies with appropriate controls.

The chapters dealing with complications discuss deep venous thrombosis, effects of immersion in patients with marginally compensated congestive heart failure, ventricular tachycardia, post-treatment hypertension, and intrarenal and perirenal hematomas. Unfortunately, because of the small sample sizes, most of these case reports have only limited usefulness in guiding patient selection.

This book will be of interest to all those working in the field and will find a place in many departmental libraries. It suggests a number of issues that deserve further study. It is clear that ESWL has revolutionized the treatment of renal stones, and the clinical experience will continue to expand. This reviewer predicts that the next symposium will be much larger and will begin to report controlled studies.

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Geriatric Anesthesia: Principles and Practice

C. R. Stephen and R. A. E. Assaf, eds. Stoneham, MA: Butterworths, 1986, 376 pp, $44.95.

As surgical intervention becomes more aggressive in the aged, an increasing number of individuals over age 65 will require anesthesia. It is therefore timely that a text such as *Geriatric Anesthesia: Principles and Practice* is available for reference. The text features 15 chapters authored primarily by

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anesthesiologists and internists from Europe, the United States and Australia.

The text opens with an excellent review of the aging cardiovascular system. In this chapter, Lakatta and Fleg present a state-of-the-art summary of physiologic changes in the cardiovascular system which have been observed in longitudinal aging studies. They disprove the long-held contention that myocardial atrophy occurs with aging and discuss the compensatory mechanisms the elderly cardiac system employs in response to stress. For instance, compared to younger individuals, the aged myocardium at rest has a slower heart rate, a higher end-systolic volume, and a reduced ejection fraction. During exercise or other stress, cardiac output in the elderly patient is enhanced not so much by tachycardia as by an increased end-diastolic volume resulting in a greater stroke volume. They emphasize the fact that aging is only one of three important factors affecting the cardiovascular system in geriatric patients; the other two are the development of cardiovascular disease and the effect of different life styles. They suggest that the hemodynamic response of elderly subjects to exercise or other stresses may be significantly improved by long term physical conditioning.

The chapter dealing with evaluation of cardiovascular risk in elderly patients reviews the morbidity and mortality of aging members of society caused by a diseased cardiovascular system. Unfortunately, this chapter does not discuss in any detail the risk cardiovascular aging produces for elderly patients undergoing anesthesia and surgery. The same criticism applies to the chapters, "Brain and Neuroendocrine System," "Aging and the Kidney," and "Alterations in Drug Disposition."

A well-illustrated chapter by Kefrak et al, provides an excellent review of the structural and functional changes of the aging respiratory system. More important, insight is gleaned as to the clinical significance of these changes for patients undergoing anesthesia and surgery. They emphasize that elderly patients are less adept at meeting respiratory demands induced by hypoxemia or increased CO_2 production. The authors further explain that the pulmonary changes of aging are similar to, but less severe than, those of emphysema. With both processes, respiratory parameters are disturbed from normal in like fashion, but a healthy aged lung may be far less afflicted than a younger lung with the disease process of emphysema.

Tasch and Stoelting render a fine review of changes in the autonomic nervous system induced by aging. They draw the attention of the anesthesiologist to the importance of this system, not just in maintaining cardiovascular homeostasis, but to the equally important function of maintaining thermal stability and make clinical suggestions as to how normothermia may be maintained in elderly patients in an operating room setting.

Adverse drug interactions during anesthesia is a topic of interest to anesthesiologists, especially as we gain an appreciation that elderly patients are frequently walking drug stores, receiving medications from multiple physicians or from over-the-counter sources. Although a general table of drug interactions may be found in the chapter by Ramadhyani and Grogono, the chapter would be significantly improved by expanding the discussion of potential adverse interactions of anesthetic agents with medications commonly consumed by the elderly.

A good, common-sense approach to preoperative evaluation and premedication of the elderly is suggested in a chapter authored by the editors of text, who describe important factors to consider preoperatively and discuss the rationale for administering or withholding preoperative medication. Similarly, Sullivan and Siker have provided insight into the potential pros and cons of regional anesthesia for the elderly, a topic worthy of elaboration.

The chapters dealing with the effects of anesthetics on the aging heart and with anesthesia management of the aged, hypertensive patient are detailed and well documented. Gravenstein and Paulus have presented a well illustrated treatise of appropriate monitoring during anesthesia. However, this chapter also fails to focus on how these monitors should be applied to elderly patients.

The concluding chapter by Stephen describes an epidemiologic study of risk factors and outcome in elderly patients. This is perhaps the topic of greatest interest to anesthesiologists today. What are the important preoperative variables that determine the eventual outcome of geriatric surgical patients? What types of anesthesia are associated with the lowest risk of morbidity and mortality in this patient population? This chapter concentrates on a single study contributing to this literature. This topic will need continued elaboration and updating as time progresses.

In summary, *Geriatric Anesthesia* provides useful information to the practicing clinician. Most of the topics addressed are discussed lucidly. The text would have been improved in many sections if more specific suggestions had been made regarding how geriatric patients undergoing anesthesia and surgery should be handled in the clinical setting. Although the text is fairly comprehensive, there are gaps in its coverage. For instance, a discussion of aging changes in the endocrine system needs to be included as does a discussion of how the use of specific anesthetic drugs may be altered in elderly patients. Finally, in light of changing hospital practices, a discussion is warranted of how geriatric patients should be managed when receiving anesthesia in either an outpatient or an out-of-operating room setting.

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Cardiovascular Actions of Anesthetics and Drugs Used in Anesthesia. Volume 1: Basic Aspects

B. M. Altura and S. Halvey, eds. Basel: S. Karger AG, 1986. 268 pp. $108.50.

This book is the first of two volumes covering the effects on the cardiovascular system of anesthetics and other drugs used in anesthesia. The editors, both noted workers in microcirculation, have set out with the laudable aim of collecting, in a critical and state-of-the-art fashion, a series of treatise that will be useful for clinicians as well as research scientists and serious students. The contributors are drawn from both North America and Europe, adding to the considerable diversity in perspectives and styles of writing.

Much of the information has been published in similar form in recent publications, with two noted exceptions. Deligne, from France, provided a detailed and updated review of neuroleptic drugs, many unfamiliar to North America, that is a welcome addition to the English literature. His eloquent defense of neuroleptic technique is thought-provoking to those weaned on "cardiovascular stability" and "pure narcotics." Philbin's chapter on neurohumoral substances released during anesthesia is a short and selective summary of this vast and exploding area of knowledge. Sonntag's discussion of narcotics is refreshing and clear.

Given the familiarity and fundamental nature of the subject matter, this reviewer chose to judge this volume against the aims and standards set forth by its editors. The aim to reach a wide readership with a book of this modest size unfortunately will make it unsatisfactory for many of its intended readers. For example, clinical and laboratory results are often not clearly delineated. The methodologic aspect of studying drug effects and interspecies variation received no separate treatment. Selection of topics is obviously limited. The laboratory worker will find no mention of chlorolase or pentobarbital, whereas the clinician will not find information on anticholinergic drugs or vasodilators.

Although most of the chapters are well-referenced, the critical element is often lacking. Some references are quoted out of context or simply misquoted. The serious reader will be well-advised to go to the actual references in key areas. Thiopental and ketamine are discussed by two authors with conflicting statements. Yet, the reader is urged by each author to consult the other for further details. This book merits a place on the library shelf for some of the chapters. However, the price will put it out of the reach of most personal budgets. Clinicians or trainees who desire a personal reference volume in this field will probably find a better bargain in other monographs.

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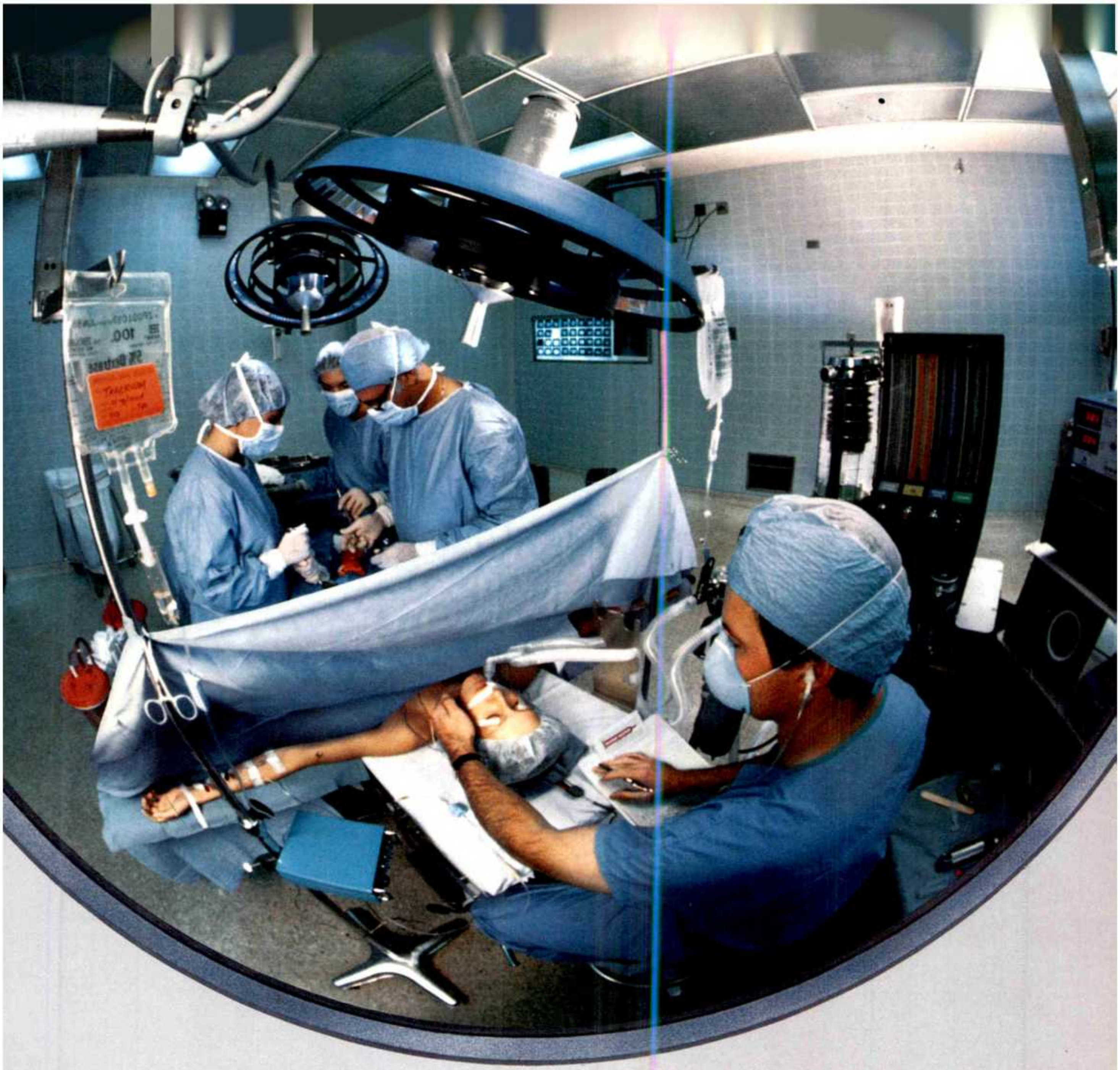

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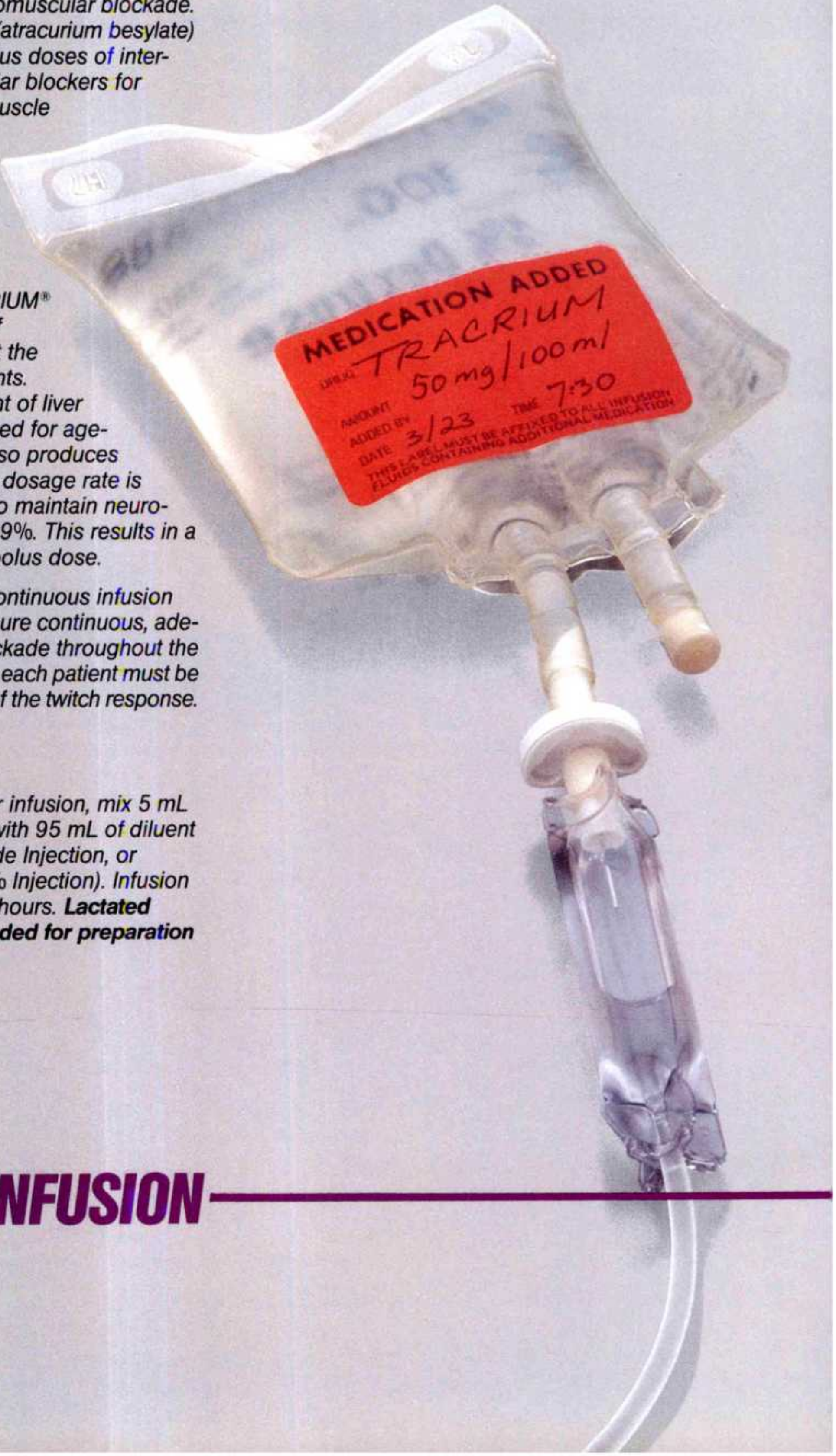
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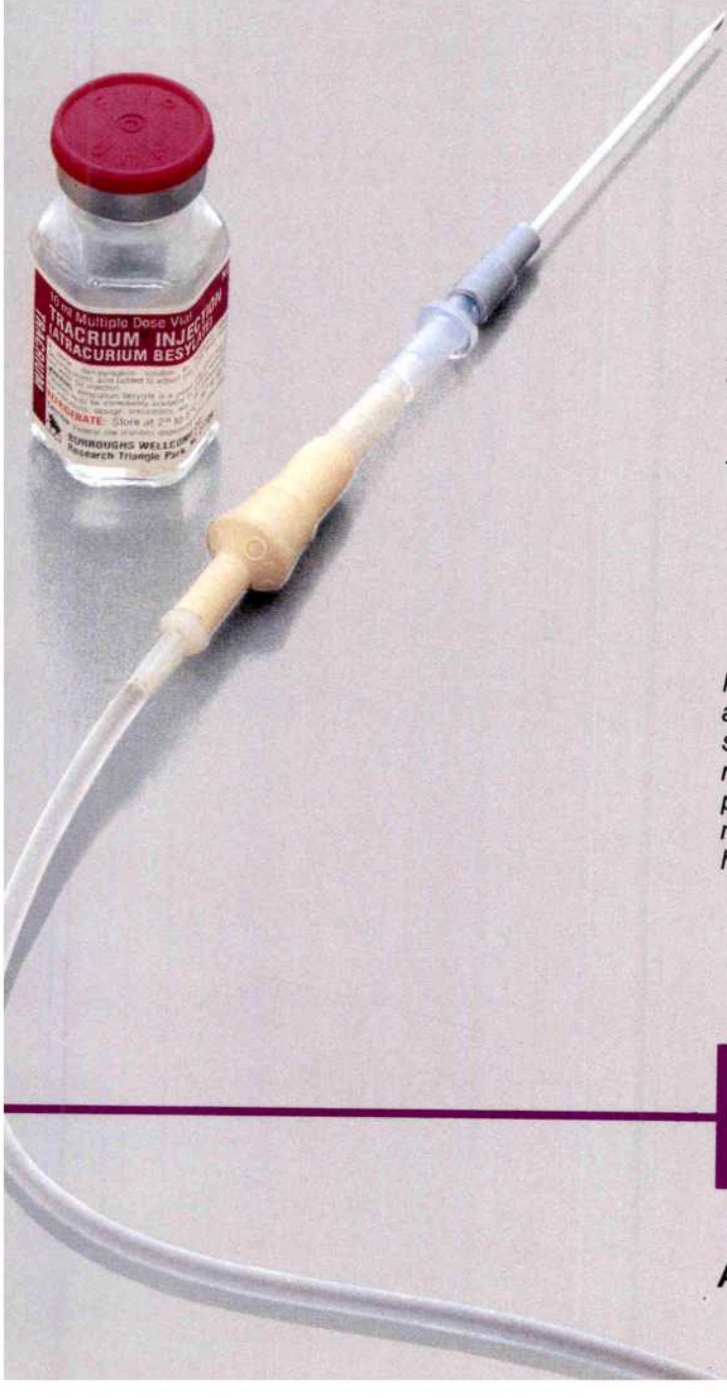

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Initial loading dose: *Administer an initial bolus dose of 0.3-0.5 mg/kg (approximately 21-35 mg in a 70 kg adult).*

Initial infusion dose: *Infuse TRACRIUM® at a rate of 9-10 µg/kg/min to maintain 89-99% neuromuscular blockade until steady-state relaxation is achieved. Dosage should be titrated to the individual patient's needs.*

Maintenance infusion dose: *Once steady-state neuromuscular blockade is achieved, an infusion rate of 5-9 µg/kg/min is adequate to maintain continuous blockade in the 89-99% range for most patients under balanced anesthesia. Occasional patients may require as little as 2 µg/kg/min, or as much as 15 µg/kg/min for maintenance.*

Dose Calculations:

TRACRIUM INFUSION DELIVERY RATE µg/kg/min	INFUSION DELIVERY RATE 0.5 mg/mL SOLUTION mL/kg/min	mL/kg/hr
5	0.010	0.60
6	0.012	0.72
7	0.014	0.84
8	0.016	0.96
9	0.018	1.08
10	0.020	1.20

Maintenance infusion rates should be reduced by approximately one-third in the presence of steady-state enflurane or isoflurane; smaller reductions are required for halothane. Hypothermia (25°C-28°C) can prolong the effect of surgical relaxation, so infusion rate should be reduced by about one-half during the hypothermic period.

TRACRIUM®

injection (atracurium besylate)

Available in cost-effective multi-dose vials

Please see brief summary of prescribing information on the following page.

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TRACRIUM® INJECTION
(atracurium besylate)

Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:

General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether the drug is excreted in human milk.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS:

Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients with 0% change in heart rate. At doses of ≥0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate.

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequent reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block. *Cardiovascular:* hypotension, tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

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Bolus Doses for Intubation and Maintenance of Neuromuscular Blockade:

Adults: A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically required neuromuscular blockade generally lasts 20 to 35 minutes under balanced anesthesia. Under balanced anesthesia, recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg, to adjust for the potentiating effects of these anesthetic agents. With halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria.

Children and Infants: No Tracrium dosage adjustments are required for pediatric patients two years of age or older. A Tracrium dose of 0.3 to 0.4 mg/kg is recommended as the initial dose for infants (1 month to 2 years of age) under halothane anesthesia. Maintenance doses may be required with slightly greater frequency in infants and children than in adults.

Special Considerations: An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for adults, children, or infants with significant cardiovascular disease and for adults, children, or infants with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated. There has been no clinical experience with Tracrium in these patients, and no specific dosage adjustments can be recommended. No Tracrium dosage adjustments are required for patients with renal disease.

Use by Infusion: After administration of a recommended initial bolus dose of Tracrium (0.3 to 0.5 mg/kg), a diluted solution of Tracrium can be administered by continuous infusion to adults and children aged 2 or more years for maintenance of neuromuscular blockade during extended surgical procedures. Infusion of Tracrium should be individualized for each patient. The rate of administration should be adjusted according to the patient's response as determined by peripheral nerve stimulation.

Infusion of Tracrium should be initiated only after early evidence of spontaneous recovery from the bolus dose. An initial infusion rate of 9 to 10 μg/kg/min may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 5 to 9 μg/kg/min should be adequate to maintain continuous neuromuscular blockade in the range of 89 to 99% in most pediatric and adult patients under balanced anesthesia.

The neuromuscular blocking effect of Tracrium administered by infusion is potentiated by enflurane or isoflurane and, to a lesser extent, by halothane. Reduction in the infusion rate of Tracrium should, therefore, be considered for patients receiving inhalation anesthesia. The rate of Tracrium infusion should be reduced by approximately one-third in the presence of steady-state enflurane or isoflurane anesthesia; smaller reductions should be considered in the presence of halothane. In patients undergoing cardiopulmonary bypass with induced hypothermia, the rate of infusion of Tracrium required to maintain adequate surgical relaxation during hypothermia (25° to 28°C) has been shown to be approximately half the rate required during normothermia.

Spontaneous recovery from neuromuscular blockade following discontinuation of Tracrium infusion may be expected to proceed at a rate comparable to that following administration of a single bolus dose.

Tracrium infusion solutions may be prepared by admixing Tracrium Injection with an appropriate diluent such as 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, or 5% Dextrose and 0.9% Sodium Chloride Injection USP. Infusion solutions should be used within 24 hours of preparation. Spontaneous degradation of Tracrium has been demonstrated to occur more rapidly in lactated Ringer's solution than in 0.9% sodium chloride solution. Therefore, it is recommended that Lactated Ringer's Injection USP not be used as a diluent in preparing solutions of Tracrium for infusion.

The amount of infusion solution required per minute will depend upon the concentration of Tracrium in the infusion solution and the dose of Tracrium desired (see table).

Tracrium (atracurium besylate)—Rates of Infusion for Concentrations of 0.2 and 0.5 mg/ml

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (ml/kg/min)	
	0.2 mg/ml*	0.5 mg/ml**
5	0.025	0.010
6	0.030	0.012
7	0.035	0.014
8	0.040	0.016
9	0.045	0.018
10	0.050	0.020

*2 ml of 1% (10 mg/ml) Tracrium Injection added to 98 ml of diluent
**5 ml of 1% (10 mg/ml) Tracrium Injection added to 95 ml of diluent

U.S. Patent No. 4179507

85TRA16

TWO COMPLEMENTARY TITLES FROM ELSEVIER

Head Injury and the Anaesthetist

edited by **W. Fitch** *and* **J. Barker**

It is believed that the anaesthetist will continue to have an important roll to play in the *overall* care of the head-injured patient, an involvement that should go far beyond the 'provision of technical assistance in the care of the unconscious patient and of anaesthesia for surgical procedures'. The contents of this monograph will inform the anaesthetist about some of the wider aspects associated with trauma to the head, and so enable him to participate fully in the care of these patients.

CONTENTS: List of Contributors. Preface. 1. The pathology of head injury *(D. I. Graham)*. 2. The patho-physiology of head injury *(J. D. Miller)*. 3. Pulmonary function in the head-injured patient *(S. Jennett)*. 4. The clinical assessment of the head-injured patient *(G. Teasdale)*. 5. The immediate care and transportation of the head-injured patient *(S. Galbraith)*. 6. Anaesthesia and the head-injured patient *(J. Barker)*. 7. The post-operative care of the head-injured patient *(J. M. Horton)*. 8. Artificial ventilation in the management of the head-injured patient *(D. G. McDowall)*. 9. Intracranial pressure monitoring in the management of the head-injured patient *(S. Galbraith)*. 10. Extracranial injuries-facial injuries *(J. P. Vance)*. 11. Extracranial injuries-chest injuries *(A. B. M. Telfer)*. 12. The use of barbiturate therapy in the management of the head-injured patient *(H. M. Shapiro, B. J. Dunlop and L. F. Marshall)*. 13. Brain death *(W. Fitch)*. 14. Future developments in the care of the head-injured patient *(B. Jennett)*. Subject index.

1985 290 pages
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International Resuscitation Days

Proceedings of the 2nd International Resuscitation Days
Rome, 2 October 1985

edited by **A. Gasparetto**

The success of the first meeting of the International Resuscitation Days inspired the organization of a second symposium upon which this book is based. The two main topics of this symposium were shock and parenchymal acute respiratory failure. Once again, great interest was elicited by original contributions dealing with the most recent advances in these two fields of intensive care. The contents of this proceedings volume will certainly constitute a valuable source of information for those working in intensive care throughout the world.

Contents: **Lectures.** The ethics of intensive care *(M. Rapin)*. Oximetry in the weaning of the ventilator patient *(O. Prakash)*. **Cellular Anoxia and Shock: An Update.** The role of the mitochondrial oxidative damage in the pathogenesis of circulatory shock in humans *(C. G. Corbucci, A. Gasparetto, M. Antonelli, M. Bufi, R. A. De Biasi, and G. Crimi)*. Mechanisms and therapy of septic shock *(L. B. Hinshaw)*. Endogenous opioids and other peptides in shock, spinal trauma and stroke *(J. W. Holaday, E. W. Bernton, R. C. Kinney, J. B. Long and D. S. Malcolm)*. Thromboxanes and leukotrienes as mediators of ischemia and shock *(A. M. Lefer)*. Do leukocytes play a role in the tissue damage seen with ischemia and injury? *(D. H. Lewis)*. Oxygen radicals in the pathogenesis of circulatory shock *(G. P. Novelli)*. Endurance exercise and shock - Role of oxygen radicals and antioxidants *(L. Packer)*. Septic shock *(W. Schumer)*. **New Concepts on Respiratory Support.** True mechanisms of new techniques for respiratory support: Observation on CPAP *(G. Damia, A. Pelizzola, M. Solca, M. Cigada, and A. Elena)*. True mechanisms of the new techniques of ventilatory support: Observations on high frequency jet ventilation *(G. Damia, A. Pelizzola, M. Solca, M. Cigada and A. Elena)*. Pathophysiological considerations on special modes of ventilation in severe respiratory distress syndrome *(B. Jonson, E. Evander, B. Lachmann and P. Wollmer)*. Clinical applications of combined high frequency ventilation (CHFV) *(G. Crimi, C. Mattia, G. Conti and A. Gasparetto)*. Rationale for independent lung ventilation in unilateral pneumonia *(F. Lemaire)*. Technical modalities for the realization of independent lung ventilation (ILV) *(U. R. Borg and J. C. Stoklosa)*. Clinical application of asynchronous independent lung ventilation (AILV) *(K. Hillman)*. Index of authors.

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Distributor in the U.S.A. and Canada:
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Other studies demonstrate that when any reduction in platelet count or prolongation of PT or PTT does occur with Hespan, no increased bleeding results, even in patients with multiple trauma.[3-5] As with any volume expander, patients should be monitored for excessive hemodilution of coagulant factors or circulatory overload when large volumes are administered.

When Hespan-treated patients were monitored to detect localized or systemic sepsis, there was no evidence of a decrease in their ability to ward off infection or combat an established infection.[5]

Hespan is nonantigenic and, as with blood-derived colloids, any risk of allergic reaction is minimal. Hespan also has a negligible effect on subsequent blood typing or crossmatching.[6]

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Comparative clinical studies have repeatedly demonstrated that Hespan is as effective as albumin or PPF in postoperative myocardial revascularization,[1-3] and hemorrhagic, traumatic, or septic shock.[4,5,7]

No significant differences between Hespan and albumin or PPF were noted in any efficacy parameter.[1,5,7] Hespan effectively maintained colloid osmotic pressure, restored plasma volume, and improved cardiac output and renal function in hypovolemic patients.[1,5,7] And, the volume-expanding effect of a single infusion of Hespan can persist for 24 hours or longer.

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References: 1. Diehl JT, Lester JL, Cosgrove DM: Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg 34* (6):674-679, 1982. 2. Moggio RA, Rha CC, Somberg ED, et al: Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med 11* (12):943-945, 1983. 3. Kirklin JK, Lell WA, Kouchoukos NT: Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg 37* (1):40-46, 1984. 4. Puri VK, Paidipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. *Crit Care Med 9* (12):833-837, 1981. 5. Shatney CH, Deepika K, Militello PR, et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. *Arch Surg 118*:804-809, 1983. 6. Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and blood crossmatching. *Transfusion 22* (3):226-228, 1982. 7. Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med 11*(11):839-850, 1983.

HESPAN® (hetastarch)

6% Hetastarch in 0.9% Sodium Chloride Injection

CONTRAINDICATIONS

Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

WARNINGS

Large volumes may alter the coagulation mechanism. Thus, administration of hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.

Usage in Leukapheresis: Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.

Usage in Pregnancy: Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.

Usage in Children: No data available pertaining to use in children.

The safety and compatibility of additives have not been established.

PRECAUTIONS

The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.

Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).

Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see ADVERSE REACTIONS). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

ADVERSE REACTIONS

The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

HOW SUPPLIED

NDC **0094-0037-05-Hespan®** (6% Hetastarch in 0.9% Sodium Chloride Injection) is supplied sterile and nonpyrogenic in 500 ml intravenous infusion bottles.

CAUTION

Federal (U.S.A.) law prohibits dispensing without prescription.

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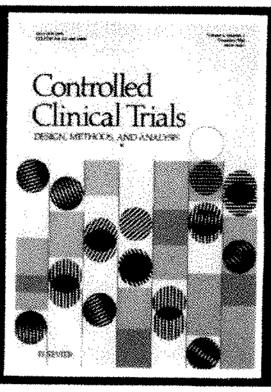

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ISSN 0197-2456

Controlled Clinical Trials is abstracted/indexed in: Biological Abstracts, Current Contents/Life Sciences, Excerpta Medica, and Index Medicus.

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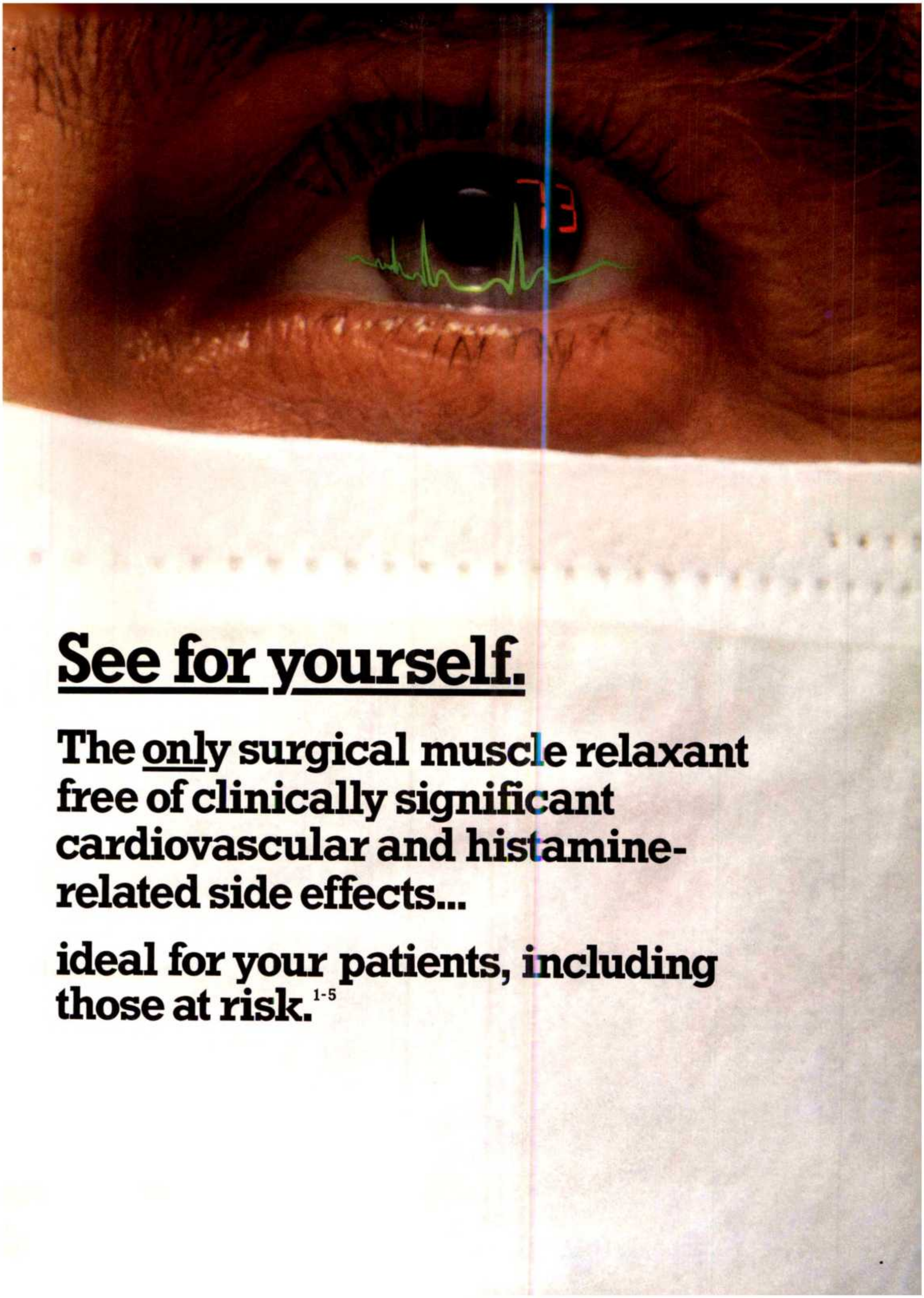

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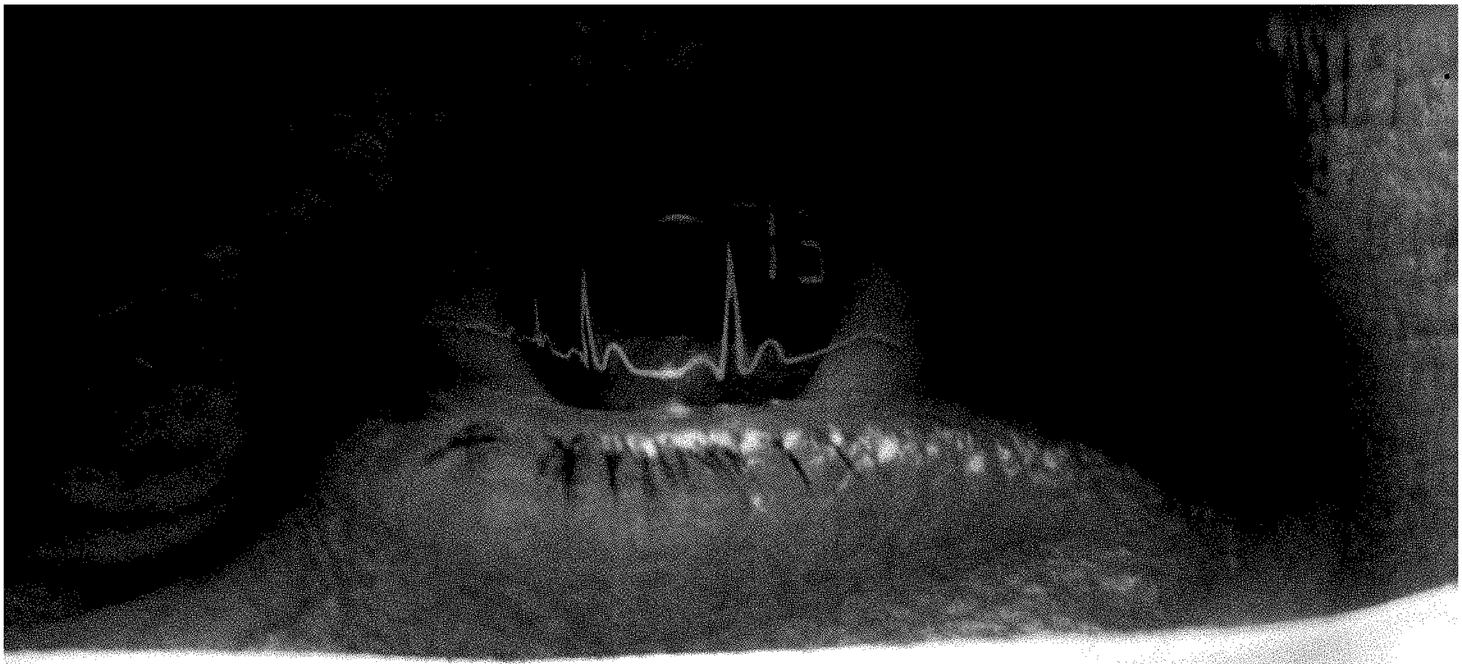
The only surgical muscle relaxant free of clinically significant cardiovascular and histamine-related side effects...

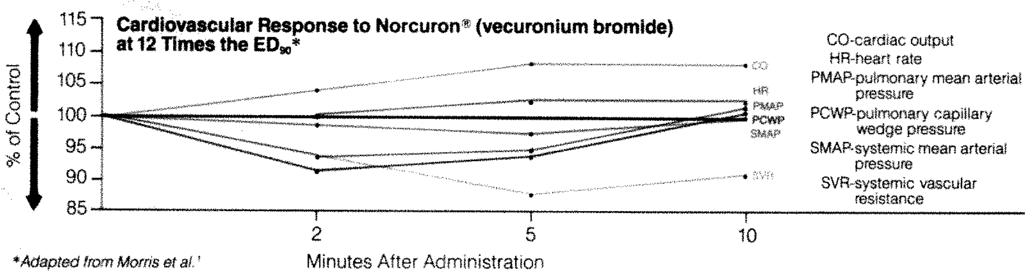
ideal for your patients, including those at risk.[1-5]



See the safety for yourself.

Free of clinically significant cardiovascular effects.*

NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials.[1-4] In fact, even at 12 times effective doses, under halothane anesthesia,[1] NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.



Cardiovascular Response to Norcuron® (vecuronium bromide) at 12 Times the ED_{90}*

**Adapted from Morris et al.[1]*

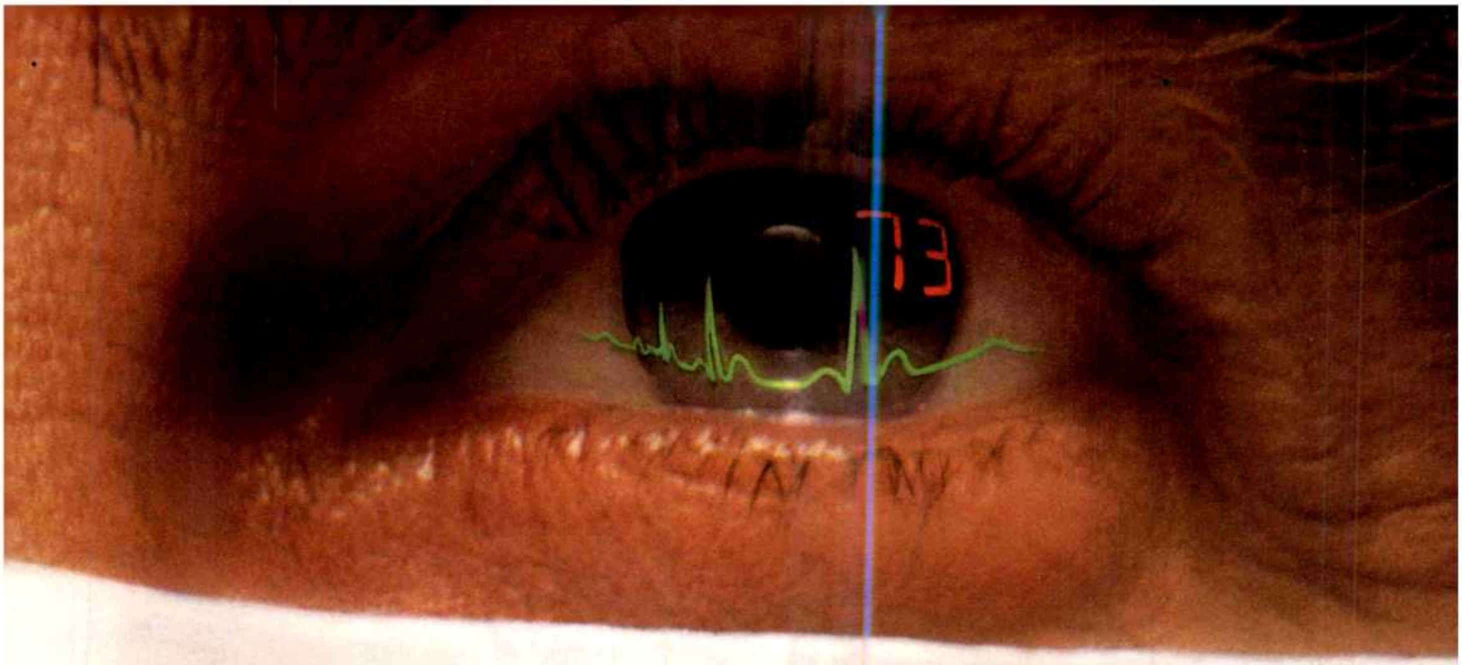
Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED_{95}.[5]

NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.[5]

The Effect of Nondepolarizing Muscle Relaxants*

Drug	Dose (mg/kg)	xED_{95}	Histamine	Mean Arterial Pressure	Heart Rate
			Percent of Control		
Tubocurarine	0.5	1	410	78	116
Metocurine	0.5†	2	212	79	119
Atracurium	0.6†	3	192	80	108
Vecuronium	0.1	1.7	117	100	99
Vecuronium	0.2	3.5	87	99	102

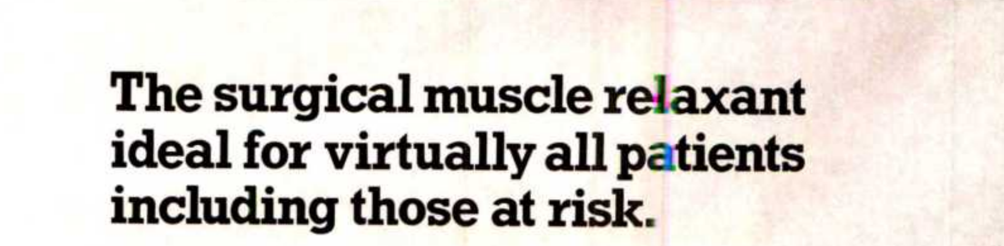
**Adapted from Basta et al.[5]*
†0.1 mg/kg higher than recommended dose.



Performance unaffected by renal function.[6]

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.[6]

Comparative Indices of Neuromuscular Blockade for Patients With and Without Renal Function Given Equal Doses (0.14 mg/kg)* of NORCURON® (vecuronium bromide) by Bolus Injection†



*Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.08 to 0.1 mg/kg.

†Adapted from Miller et al.[6]

The surgical muscle relaxant ideal for virtually all patients including those at risk.

Norcuron®

(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. **2.** Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. **3.** Krieg N, Crul JF, Booij LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. **4.** Gallo JA, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. **5.** Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. **6.** Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide).* Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about ⅓ more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTANT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain theshold or cerebration. Administration must be accompanied by adequate anesthesia.

NO REFRIGERATION REQUIRED

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
5% glucose in saline
Lactated Ringer's

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 10 (NDC#0052-0442-17).

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STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION. SINGLE USE VIALS.

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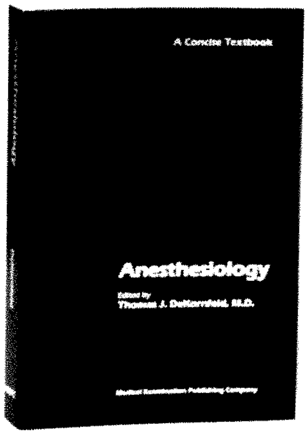

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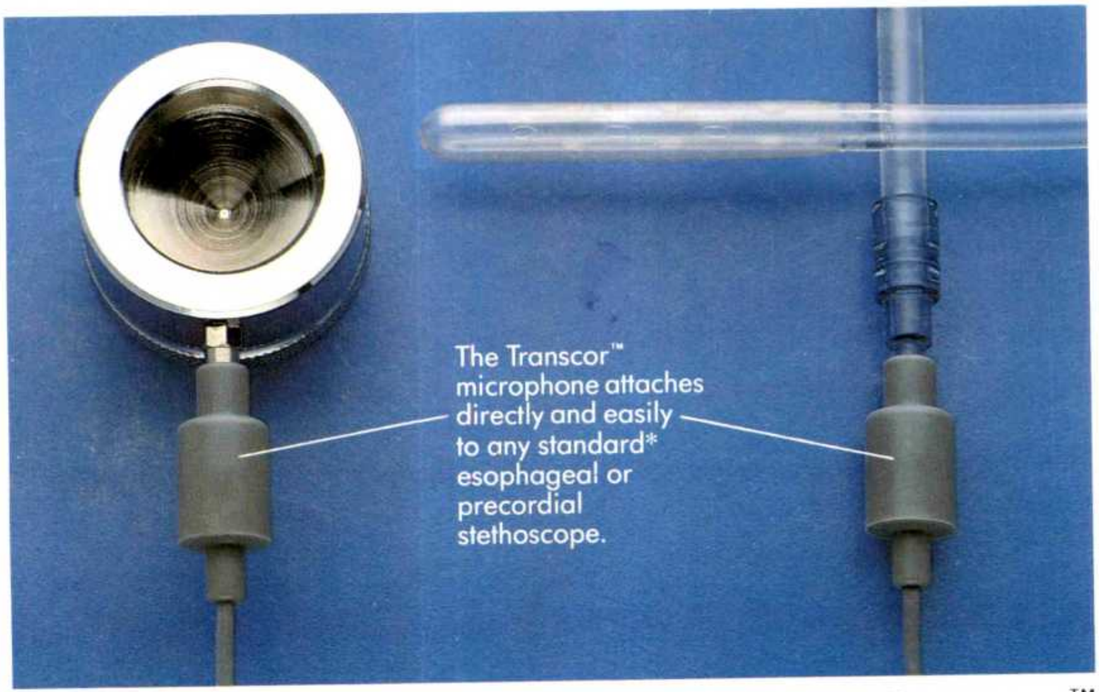
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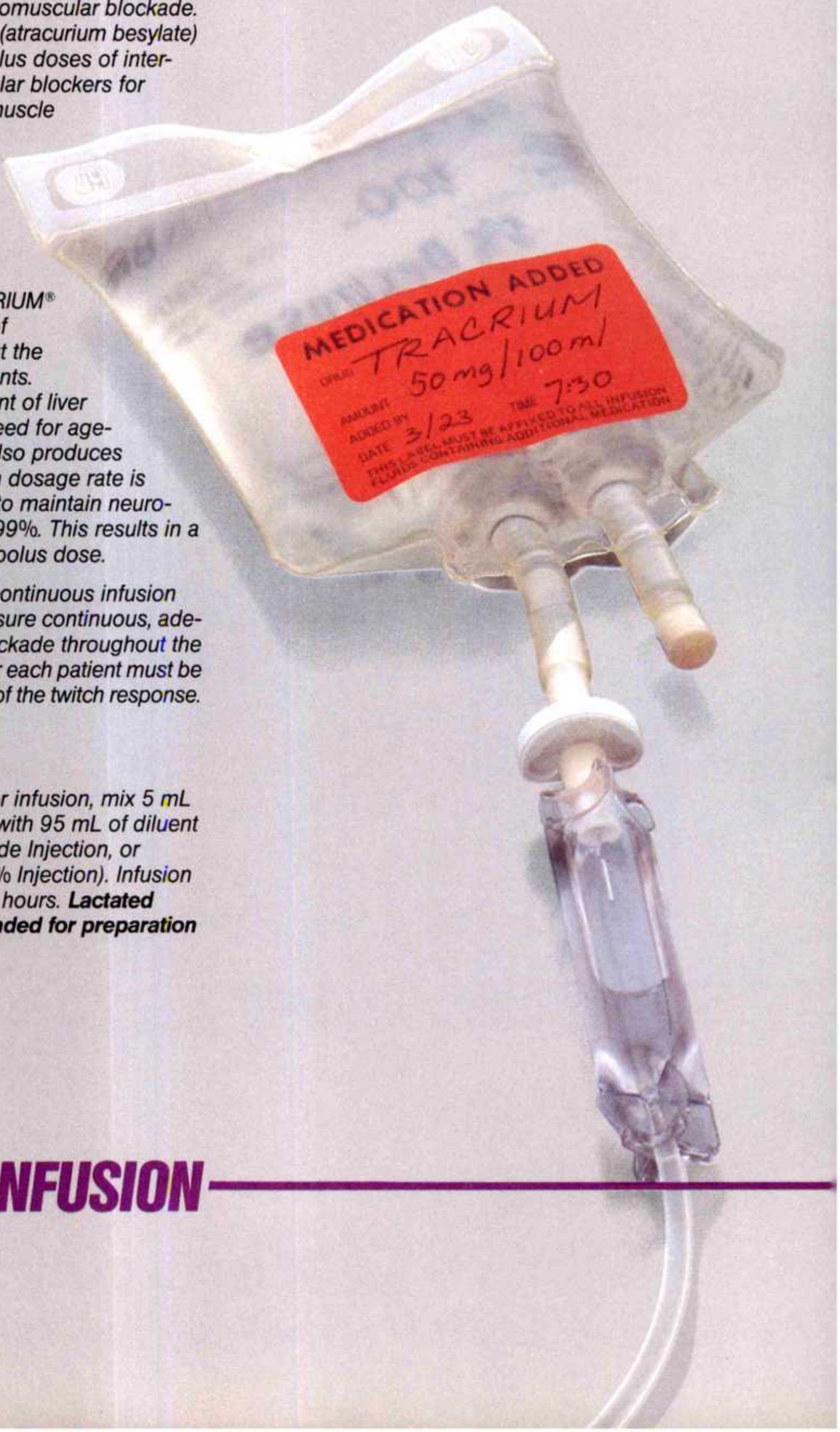
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Abstracts of Papers and Posters Presented at the International Anesthesia Research Society 61st Congress

Lake Buena Vista, Florida
March 14–18, 1987

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Journal of the International Anesthesia Research Society

Title: EFFECTS OF ISOFLURANE AND OXYTOCIN ON GRAVID HUMAN UTERUS IN VITRO

Authors: Adel R. Abadir, M.D., Shaesta G. Humayun, M.D., David Calvello, M.D., and Jonas Gintautas, M.D., Ph.D.

Affiliation: Anesthesiology Research Laboratories, Department of Anesthesiology, Brookdale Hospital Medical Center, Brooklyn, New York

Introduction. Isoflurane (1-chloro-2,2,2-triflurroethyl ether) is a well accepted inhalation anesthetic agent used in everyday clinical practice. The agent is relatively insoluble in blood, usually produces minimal hemodynamic changes, facilitates neuromuscular blockade, and depresses cerebral activity. There are a limited number of publications reporting the depression of contractibility of human uterine muscle by isoflurane in vitro and in vivo (1,2). Blood loss during dilation and evacuation or during delivery was related to isoflurane effect (3). Oxytocin, a synthetic polypeptide, is used to elicit uterine contractions or to control uterine bleeding. The information regarding the isoflurane and oxytocin combined effect on human uterus is limited. In this study we examined the effect of isoflurane on isolated gravid human myometrium and demonstrated the reversibility of this effect.

Method. Thirty uterine specimens were obtained from ten gravid patients undergoing repeat caesarian sections. The mean age was 29 years (range 21-49) and mean parity was 2. The study was approved by the Research and Clinical Projects Committee. Uterine muscle tissues were collected during C-sections. The specimens were cut 15 x 2 x 1mm and individually suspended in 50ml double jacket glass chambers filled with physiological solution having the folowing composition in mM/l:NaCl,110; $NaHCO_3$, 24, KCl, 5.0; $Na_2HPO_4 7H_2O$, 1.1; $CaCl_2$, 2.2; $MgSO_4$, 1.2; glucose, 5.5. The buffer was adjusted to pH 7.4, temperature of the solution was maintained at 37 degrees celsius, and aerated with a mixture of 95% O_2 and 5% CO_2. Isometric tension was measured and recorded using grass FT03 force transducers and 7 D polygraph. The tissues were exposed to five consecutive 40 minute periods of 0.5%, 1.0% and 1.5% isoflurane. Oxytocin (0.2 uu/ml) was used to reverse 1.5% isoflurane induced relaxation. In each myometrial tissue we measured the number of contractions, the mean peak tensions (in grams), the mean interval between contractions and the uterine activity (in Montevideo units). Analysis of variance and Dunnett's statistical method were used to test differences between self control values in all strips and values in each of the four time periods. Unpaired student's t-test was used for differences between experimental and time control strips.

Results. Susceptability of gravid human myometrial tissues to isoflurane is reflected in the dose-response curve (table 1). The data show that the concentration of isoflurane required to inactivate 50 percent of isolated gravid human myometrial strips is 1.4 percent. Isoflurane, at dosages tested, significantly reduced the frequency of contractions and increased the interval between contractions (p 0.05). Peak tension tended to increase but reached significance, as compared to self control period, only during time period 4 (1.5% isoflurane). All concentrations of isoflurane caused a significant decrease in uterine activity (p 0.05). Using clinically equivalent dosages of oxytocin (15 u units/bath) it was possible to reverse the inhibitory effect of isoflurane even at 1.5 percent concentration.

General Conclusion. Our results demonstrate that isoflurane depresses the contractility of the isolated human uterine muscle. The present data is consistent with previous reports that isoflurane produces depressant effect on pregnant mammalian myometrium (1,2). CLinically applicable dosages of oxytocin reverse the inhibition and thus oxytocin may be used to reverse undesirable isoflurane effect.

References.
1. Munson, E.S., & Embro, W.J.: Enflurane, isoflurane, and halothane and isolated human uterine muscle. Anesthesiology 1977;46: 11-14
2. Munson, E.S.: Isoflurane, M.E.J. Anesth. 1981 6(4) 181-188. 3. Dolan, W.M., EGER, E.I. II, Margolis, A.J. Forane increases bleeding in therapeutic suction abortion. Anesthesiology 1972 36:96-97

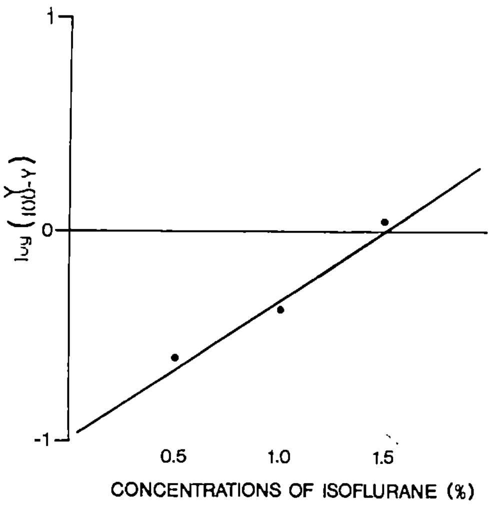

Figure 1. Dose-response curve based on three levels of isoflurane concentrations. The line is the result of regression analysis (r = 0.98). Vertical axis is the transformation of the sigmoid curve (y = % of inactivated gravid strips). Horizontal axis corresponds to the values of the isoflurane concentrations.

Title: IMMEDIATE DETECTION OF CRITICAL TRANSIENT HYPOXIC EPISODES IN ACUTE HEAD INJURIES

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Introduction. One of the major goals in the treatment of acute head injuries is to prevent further cerebral insults (secondary injuries) such as inadequate oxygen delivery to the brain. Therefore, the detection of all kinds of hypoxia is important in the management of these patients. Unfortunately, no simple clinical tool exists for the determination of these events. The objective of this study was to evaluate continuous monitoring of arterial-jugular venous oxygen saturation difference (AJDSO2) as a simple, reliable bedside technique for patients with acute head injuries.

Methods. Following approval of the Committee for the Protection of Human Subjects and informed consent from the family, 16 adult patients with Glasgow Coma Scores of 4-7 following acute head injuries (with head CT scans indicating little or no midline shift) served as the study subjects. An intracranial pressure (ICP) monitor was implanted and hyperventilation begun. In addition, sedation (16 patients), muscle relaxants (16), mannitol (15), barbiturate coma (3), cerebral spinal fluid drainage (5), and decompressive craniotomy (1) were used to keep ICP below 20 mmHg. Mean arterial blood pressure (MAP), End-expired CO2 (PeCO2), and ICP were continuously recorded postoperatively in the SICU. Arterial (SaO2) and jugular venous (SjvO2) oxygen saturation were continuously measured via 4 Fr fiberoptic oximetry catheters in a femoral artery and the superior portion of a jugular bulb. An alarm was set on the arterial oximetry monitor to respond to decreases in SaO2 below 90%. Cerebral oxygen extraction was estimated by the (AJDSO2).

Two types of hypoxic problems occurred in these patients. Oligemic hypoxia is defined as a condition where the AJDSO2 (normal < 30%) becomes greater than 40%. If cerebral oxygen delivery is decreased excessively by hyperventilation, then the amount of oxygen extracted will be greater and the AJDSO2 will rise. Patients with ICP below 20 mmHg, but AJDSO2 of > 40%, were managed by raising the PeCO2 followed by mannitol boluses, if the ICP rose above 20 mmHg. If the AJDSO2 was > 40%, but the ICP was ≥ 20 mmHg, then mannitol was given and PeCO2 was not adjusted. Hypoxemic hypoxia exists when SaO2 decreases < 90%. When the preset alarm was activated by SaO2 < 90%, patients were promptly treated by increasing the fraction of inspired oxygen (FiO2) and the patient and ventilator inspected.

Results. Hypoxemic hypoxia - Fifty three episodes were identified in 13 patients in the first 72 hours post-injury. Of these early events, 31 were related to an identifiable pulmonary or ventilatory problem, while 22 (42%) occurred in the absence of any definable event. In every case, the hypoxemia responded immediately to an increase in FiO2. Typically, the SaO2 would fall precipitously, without any other clinical indication, followed by a drop in the SjvO2 30-45 seconds later. Only one episode seemed to be triggered by an acute rise in ICP.

Oligemia hypoxia - When monitoring was initiated, all patients had normal CPP (MAP-ICP). However, we found that routine hyperventilation was associated with oligemia in eight (50%) patients. All oligemic episodes were satisfactorily resolved by the above protocol. For example, at the initiation of monitoring in one patient, the ICP was 18, but the AJDSO2 was 65%. Increases in PeCO2 resulted in an improvement in the AJDSO2, but also an increase in the ICP above 20 mmHg. The administration of two mannitol boluses brought about the desirable effects of a reduction in ICP and a further rise in SjvO2.

Conclusion. The results of this study demonstrate that AJDSO2 is a valuable bedside monitor of simple design that can detect critical cerebral oxygen delivery changes. Our results also indicate that sudden, unexpected arterial desaturation is a common occurrence in the first 72 hours following acute head injuries. Further, 42% of the early hypoxemic episodes were self-limiting, but of unknown etiology. These early episodes responded immediately to transient increases in FiO2 in every case. In addition, we found that with the use of routine hyperventilation, the incidence of oligemic hypoxia was 50%. Normalized AJDSO2 and control of ICP were achieved in each of these cases by reducing hyperventilation and/or infusion of mannitol. Continuous AJDSO2 monitoring in the patient with acute head injury is a useful clinical tool for the immediate identification and resolution of dangerous hypoxic episodes.

References

1. J Neurosurg 1984; 61:241.

Title: VECURONIUM PHARMACOKINETICS AND PHARMACODYNAMICS IN HEPATOCELLULAR DISEASE

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Introduction. Because of the extensive hepatic uptake of vecuronium (VEC), its duration of action may be prolonged in patients with liver disease. Lebrault et al (1) found clearance reduced and duration of action prolonged after a large dose of VEC (0.2 mg/kg) in cirrhotic patients. In contrast, Hunter et al (2) found either no change or a shorter duration of action with VEC doses < 0.15 mg/kg in cirrhotic patients; he did not study pharmacokinetics in these patients. We therefore examined the pharmacokinetics (PK) and pharmacodynamics (PD) of a lower dose of VEC in patients with hepatic dysfunction.

Methods. After obtaining Human Studies Committee approval and informed consent, we studied sixteen elective surgical patients: nine patients with normal liver function (age 38 ± 7 yrs, wgt 73 ± 14 kg) and seven with alcohol-induced hepatocellular disease (age 46 ± 10 yrs, wgt 63 ± 7 kg). Liver disease was defined as biospy-proven cirrhosis (6 patients) or > 50% elevation of transaminases (1 patient). After premedication with diazepam, patients were anesthetized with thiopental 3-4 mg/kg i.v. and by inhalation of isoflurane with N_2O/O_2, and the trachea was intubated. Ventilation was controlled with end-tidal PCO_2 = 35-40 mmHg, end-tidal isoflurane 1-1.5% and nasopharyngeal temperature 35-37°C. We recorded force of thumb adduction in response to supramaximal ulnar nerve stimulation at 0.1 Hz. After baseline recording, VEC 0.1 mg/kg was administered as an i.v. bolus. Venous blood was collected at frequent intervals. Blood was heparinized and stored on ice briefly; plasma concentration of VEC and its metabolities were measured by gas chromatography, which was sensitive to ~5 ng/ml of the parent drug. Plasma concentration-time data were fit by a three-compartment model using nonlinear regression, Standard pharmacokinetic parameters were calculated. A BMDP statistical package was used for t-tests and correlations.

Results. PK and PD data are summarized in tables 1-2. Complete PK data was obtained for 16 patients. We found no significant difference in any PK values between patients with and without hepatic disease. PD data were obtained for 16 patients. PD data were similar for both groups with the exception of the time to achieve 100% block (Peak) which was longer for patients with liver disease than for control. For 13 patients with recovery data, plasma clearance correlated significantly with the time to beginning of recovery (r = -.78). One patient from each group showed no recovery at > 60 min. Recovery data was not complete for all hepatic patients because of surgical requirements.

TABLE 1. PHARMACOKINETIC VALUES (Mean ± SD)

	Clearance (ml/kg/min)	Vdss (l/kg)	t1/2 elim (min)
Normal (n = 9)	4.7 ± 1.9	0.17 ± 0.7	67 ± 32
Hepatic (n = 7)	3.8 ± 0.9	0.23 ± 0.1	81 ± 43

TABLE 2. PHARMACODYNAMIC VALUES (Mean ± SD)

	Peak * (min) (100% block)	Recovery of Control Twitch Tension (min) (begin) **	(25%)	(50%)
Normal	1.8 ± .5 (n = 9)	44 ± 22 (n = 8)	58 ± 26 (n = 8)	72 ± 31 (n = 8)
Hepatic	3.0 ± .7† (n = 7)	33 ± 12 (n = 5)	44 ± 15 (n = 4)	65 ± 32 (n = 3)

* = time from administration of VEC to peak effect
** = time from administration of VEC to appearence of first twitch
† = $p < .005$

Discussion. These data suggest that, when given in the recommended dose (0.1 mg/kg), VEC clearance and duration of action are unaffected by hepatocellular disease. Hunter (2) showed no effect on the duration of action of lower doses of VEC in cirrhotic patients, but did show prolonged effect at higher doses (0.2 mg/kg). Lebrault (1) suggested decreased clearance as a mechanism for prolonged effect following higher doses in cirrhotics. Our data show that duration of effect correlates with clearance. Thus, VEC may have dose-dependent clearance (non-linear PK) in patients with liver disease. This could be due to a limited hepatic uptake capacity which is exceeded after doses of VEC greater than 0.15 mg/kg. We conclude that with a dose of 0.1 mg/kg, hepatic dysfunction does not affect the pharmacokinetics or duration of action of vecuronium.

References.

1. Lebrault C, Berger JL, D'Hollander AA, et al: Pharmacokinetics and Pharmacodynamics of Vecuronium in Patients with Cirrhosis. Anesthesiology 62:601-605, 1985.
2. Hunter JM, Parker CJR, Bell CF, et al: The Use of Different Doses of Vecuronium in Patients with Liver Dysfunction. Br J Anaesth 57:758-761, 1985.

Title: HEART RATE AND RHYTHM DURING INDUCTION OF ANESTHESIA WITH PENTOTHAL AND HALOTHANE IN CHILDREN

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Introduction: The increased frequency of dysrhythmias and bradycardia during induction of anesthesia in children is related to several factors, including the anesthetic drugs administered and the induction technique used. The purpose of this study was to compare the effect of three different anesthetic regimens: 1) pentothal, 2) halothane, and 3) halothane with pentothal on the heart rate and rhythm in children.

Methods: Ninety-one children, ages 1-10 years, ASA I or II, scheduled for elective surgery were studied after approval from our Human Subject Review Committee. Before induction of anesthesia, a blood pressure cuff, precordial stethoscope and continuously recorded lead II electrocardiogram were applied. The children were assigned to one of three induction groups: 1) pentothal (STP) n = 68, 2) halothane (H) n = 13, and 3) halothane and pentothal (H/STP) n = 10. The children in the STP group were induced with iv pentothal (5 mg/kg), atropine (0.02 mg/kg) and succinylcholine (1.5 mg/kg). The children in the H group were induced with 70% nitrous oxide/oxygen and halothane (up to 3% inspired) by face mask and were given iv atropine and succinylcholine before intubation. The children in the H/STP group were induced with nitrous oxide/oxygen/halothane (up to 3% inspired) and iv pentothal (3 mg/kg), atropine, and succinylcholine before intubation. End-tidal PCO$_2$ (PetCO$_2$) was measured by infrared analysis immediately after intubation. The incidence and type of dysrhythmias, heart rates, PetCO$_2$ values and corrected Q-T intervals (Q-Tc) among and within groups were compared using the Fisher-exact test, one- and two-way ANOVA and Student-Newman-Keuls test. Statistical significance was accepted at $p \leq 0.05$.

Results: The incidence of dysrhythmias was greater in the H group (85%) than in the STP group (6%) and H/STP group (20%) (Table 1). Nodal rhythm and ventricular bigeminy were the most frequent dysrhythmias. Although the slowest heart rate during induction did not differ from pre-induction values in any of the groups, heart rate was slower in the H and H/STP groups compared to the STP group (Table 2). The PetCO$_2$ was greater in the H and H/STP groups compared to the STP group. The Q-Tc intervals were prolonged in the H group with dysrhythmias and in the H/STP group without dysrhythmias compared to pre-induction values (Table 3).

Discussion: The absence of Q-Tc prolongation and the lower incidence of dysrhythmias in children anesthetized with pentothal compared to those anesthetized with halothane alone is consistent with previous evidence which suggests that pentothal attenuates the sympathetic response to the induction of anesthesia.[1] Furthermore, in the present study, fewer dysrhythmias occurred in the H/STP group compared to the H group despite prolongation of Q-Tc in both groups. These data suggest that induction of anesthesia with pentothal may prevent dysrhythmias by attenuating the sympathetic response. It is also suggested that the lower PetCO$_2$ in the STP group provided some protection against dysrhythmias. Since there were fewer dysrhythmias and the heart rate was stable in the STP group, induction of anesthesia with pentothal is appropriate when it is desirable to avoid cardiac rhythm disturbances in children.

References:
1. Joyce JT, Roizen MF, Eger EI, II. The effects of thiopental induction on sympathetic activity. Anesthesiology 1983;59:19-22

TABLE 1

	AGE	DYSRHYTHMIAS			
		INCIDENCE	NR	VB	VEB
STP	4.4 ± 2.4	4/68	3	0	1
H	4.3 ± 2.1	11/13*	6	5	2
H/STP	5.8 ± 3.1	2/10	0	1	1

Data for age are mean (years) ± SD
INCIDENCE = number with dysrhythmias/total number of children
NR = nodal rhythm; VB = ventricular bigeminy; VEB = ventricular ectopic beats
*$P \leq 0.05$ compared with STP and H/STP groups

TABLE 2

	HEART RATE		PetCO$_2$
	PRE-INDUCTION	SLOWEST DURING INDUCTION	IMMEDIATELY AFTER INTUBATION
STP	125 ± 34	127 ± 29	35 ± 4.7
H	111 ± 23	97 ± 19*	47 ± 5.3*
H/STP	115 ± 30	101 ± 25*	42 ± 7.0*

Data are mean (bpm and mmHg) ± SD
PETCO$_2$ = end-tidal PCO$_2$
* $P \leq 0.05$ compared with STP group

TABLE 3
Q-Tc INTERVALS

TIME	STP		H		H/STP	
	DYS	NO DYS	DYS	NO DYS	DYS	NO DYS
PRE-INDUCTION	413 ±35	425 ±37	402 ±27	416 ± 1	467 ±44	454 ±45
ONSET OF DYSRHYTHMIA	404 ±50	438^{+} ±35	448* ±70	473^{+} ±14	516 ± 4	538^{*+} ±34

Data are mean (msec) ± SD
DYS, NO DYS = with, without dysrhythmias respectively
$^{+}$ Q-Tc for children without dysrhythmias at the average time for the onset of those with dysrhythmias
* $P \leq 0.05$ compared with pre-induction values

Title: ANTAGONISM OF POST-OPERATIVE OPIOID INDUCED RESPIRATORY DEPRESSION: NALBUPHINE VS. NALOXONE

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Introduction. Numerous experimental and clinical reports document the reversal of opioid-induced respiratory depression with nalbuphine (Nb). Although authors suggest that Nb may be superior to naloxone (Nx) for this purpose, others remain skeptical. Since we could find no double-blind clinical comparison of the two drugs as opioid antagonists, we decided to perform such a study in the immediate post-operative period.

Methods. The protocol was approved by the institutional review board and informed consent was obtained from 80 ASA I-III patients scheduled for elective general, orthopedic or gynecologic surgery. Patients with a history of opioid analgesic use as well as patients having oral or any respiratory system related surgery were excluded. Preoperative medication was left to the discretion of the clinical anesthesia care team. Anesthetic induction consisted of preoxygenation with 100% O_2 for 3 min, 15 ug/kg of fentanyl IV over 2 min, and 1-4 mg/kg of sodium pentothal IV as required. Muscle relaxation was produced with succinylcholine, 1.5 mg/kg IV, after a defasciculating dose of a nondepolarizing agent. All patients were orotracheally intubated and anesthesia was maintained with 60% nitrous oxide, 40% oxygen and additional fentanyl, 100-200 ugs IV per hour. Isoflurane, 0.1-1.0%, and nondepolarizing muscle relaxants were used in addition if required. Patients were mechanically ventilated to maintain an end-tidal CO_2 of 40±2 mm Hg (Hewlett Packard 47210A capnometer). Isoflurane was discontinued 5-10 min before the end of surgery. After muscle relaxation was reversed with edrophonium and atropine, and a normal train-of-four and tetanus were sustained to peripheral nerve stimulation, N_2O was discontinued. The patient was then mechanically ventilated with 100% O_2 for an additional 2 min after which time mechanical ventilation ceased. At this time respiratory rate (RR), tidal volume (TV), end-tidal CO_2 ($P_{ET}CO_2$), blood pressure, heart rate, and the presence or absence of dysrhythmias were recorded and considered as baseline values for study purposes. If apnea persisted for another 2 min or spontaneous ventilation was inadequate (rate < 8 or TV < 4 ml/ kg), the patient was enrolled in the study and either Nx, 0.08 mg, or Nb, 2.5 mg, was given IV in a double-blind manner. Every 2 min the above data were collected and the same doses of antagonist were given until adequate spontaneous ventilation (RR > 7 and TV ≥ 4 ml/kg) was sustained and the patient extubated. Prior to the onset of adequate spontaneous respiration, ventilatory assistance was given if O_2 saturation, via peripheral pulse oximetry (Nelcor pulse oximeter), was $< 90\%$ or if $P_{ET}CO_2$ was > 55 mm Hg. Arterial blood gases (Radiometer Copenhagen ABL-2) were obtained with the onset of spontaneous respiration and 30 and 60 min later. In the recovery room HR, BP, RR, TV, and the presence or absence of dysrhythmias were recorded every 5 min as were analgesic requirements. Analgesics were administered by the recovery room nurses in their standard manner Renarcotization, defined as RR < 8 in a non-stimulated patient, was also documented and treated with Nx, 0.08 mg IV. Statistical analysis was done using Hotelling t-square, unpaired t-tests and Chi-square. P values less than 0.05 were considered as statistically significant. Number values below are mean ± SEM.

Results. Fifty-two of 80 patients required opioid antagonism. Demographic data were similar in both groups. The dose of fentanyl received (Nx: 24.9 ± 1.6 ug/kg; Nb: 24.9 ± 1.2 ug/kg) and duration of anesthesia (Nx: 179 ± 16 min; Nb: 165 ± 14 min) were not statistically different for the two groups. The time from the termination of mechanical ventilation to extubation was 6 ± 2 min in the Nx group and 7 ± 3 min in the Nb group. Patients required 1.8 ± .6 doses of Nx (0.08 mg/dose) vs. 2.3 ± 1.4 doses of Nb (2.5 mg/dose). Vital signs starting with the termination of mechanical ventilation and during reversal are in Table I and no statistical differences were found between the two groups.

Table I. Vital Signs Min After Stopping Mechanical Ventilation

		0	2'	4'	6'
	SBP	108 ± 4	108 ± 2	119 ± 25	128 ± 27
Nx	HR	63 ± 2	66 ± 3	80 ± 5	83 ± 7
Group	RR	0	0	6.9 ± 1.4	13.3 ± 1.6
	TV	0	0	243 ± 57	553 ± 81
	SBP	114 ± 3	114 ± 4	124 ± 4	137 ± 7
Nb	HR	61 ± 2	65 ± 3	79 ± 5	81 ± 3
Group	RR	0	0	6.7 ± 1.4	11.3 ± 1.8
	TV	0	0	232 ± 66	504 ± 101

No difference existed in the pH, PaO_2, or $PaCO_2$ when spontaneous respiration began or 30 and 60 min later, Table II.

Table II. $PaCO_2$ For One Hour Following Reversal

	Onset of Spont. Resp.	30 min	60 min
Nx Group	48.7 ± 2.0	44.5 ± 2.1	41.2 ± 2.1
Nb Group	50.3 ± 2.0	43.2 ± 1.3	42.4 ± 0.9

Similarly there were no differences in the vital signs in the recovery room. Two patients experienced PACs (both in the Nx group) in the RR that were of no hemodynamic consequence. Only 4 patients required additional opioid antagonist in the recovery room, 3 of which were in the Nx group. Although twice as many patients reversed with Nx required analgesics in the recovery room than did those reversed with Nb (10 vs 5), this difference did not reach statistical significance.

Discussion. The results of this study demonstrate that naloxone and nalbuphine are indistinguishable when titrated IV as narcotic antagonists after large doses of opioids. Both produced similar changes in HR and SBP and adequate reversal of respiratory depression. While neither guarantees absence of renarcotization, this problem occurred in only 1 of 26 patients reversed with Nb. Patients reversed with Nx may require analgesic therapy more frequently than those receiving nalbuphine.

Title: COMPARATIVE INFUSIONS OF VECURONIUM AND THE NEW RELAXANT BW B1090U

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Introduction

BW B1090U is a short-acting nondepolarizing relaxant currently in clinical trials.[1] It is rapidly hydrolyzed by human plasma cholinesterase. Its duration is twice that of succinylcholine at intubating doses and half that of atracurium and vecuronium at equipotent doses. BW B1090U is readily reversible by anticholinesterases. This paper explores the use of BW B1090U by infusion and compares this with infusion of both vecuronium (this study) and atracurium (by reference).

Methods

Fifteen ASA I-II patients aged 18-49 years were studied with BW B1090U after obtaining institutionally approved written informed consent. Nine ASA I-II patients aged 18-49 years were studied with vecuronium after oral informed consent. All patients were premedicated with diazepam 0.10 mg/kg p.o. and morphine 0.1 mg/kg i.m. Anesthesia was induced with thiopental 4-8 mg/kg and fentanyl 4-6 μg/kg IV. Maintenance was with 66% nitrous oxide in oxygen and ventilation was controlled to maintain normal $PaCO_2$. Intubation of the trachea was accomplished following BW B1090U or vecuronium. Further thiopental and fentanyl were given to control arterial pressure and heart rate. Force of thumb adduction was transduced and recorded continuously in response to supramaximal ulnar nerve stimulation at 0.15 Hz. After stable controls were obtained, neuromuscular blockade was induced. The 1090U group received a bolus dose of 0.2 mg/kg. Recovery times were measured at 5-95% and 25-75%. When the evoked response spontaneously recovered to 95%, block was reinduced with 0.15 mg/kg of 1090 IV. When the response had returned to 5% of control, an infusion was begun to maintain blockade at 95-99%. The vecuronium group received an initial bolus of 0.1 mg/kg I.V. and when blockade was beginning to recover, an infusion was begun to maintain block at 95-99%. All infusions lasted one to two hours and were allowed to recover spontaneously. Recovery times were measured as shown in the table. Data were analyzed using both correlated and uncorrelated t-tests with $p < 0.05$ considered significant.

Data

The following table summarizes the results. Referenced data for atracurium are shown for comparison. Results are ± SE.

		Recovery Time (min)		
Drug	Infusion Time (min)	off - 25%	25-75%	5-95%
1090 (n=15)	Initial Bolus	---	6.8 ±0.4	14.2 ±0.5
1090 (n=15)	84.2 ±3.9 (60-106)	5.25 ±0.4	6.3 ±0.2*	13.9 ±0.6*
Vecuronium (n=9)	95.2 ±8.6 (56-107.5)	12.7 ±1.3**	13.3 ±0.9**	30.0 ±1.2**
Atracurium[2] (n=11)	93.2±6 (58.2-117.5)	---	9.8	25.1

* NS vs Single Bolus
** $p < 0.001$ vs BW B1090U single bolus and infusion

Discussion

BW B1090U exhibits admirable clinical characteristics when used to maintain neuromuscular blockade via the infusion method. The blockade is noncumulative, predictable, and of half the duration of atracurium and vecuronium. Further, Ramsey et al[3] found in their infusion study of succinylcholine under N20-02-narcotic anesthesia, 24 of 32 patients developed phase II block. Twelve recovered from 5-95% spontaneously in 15.0±3 minutes, which compares favorably with BW B1090U. However, the remaining 50% of Ramsey's patients had not spontaneously recovered to more than 75% of control in 31.0±5 minutes and required anticholinesterase reversal. Thus, BW B1090U appears to possess superior clinical characteristics when used by infusion compared to those agents currently available. This may prove especially desirable for day surgery and longer procedures where rapid spontaneous recovery is important.

References

1. Basta SJ, Savarese JJ, Ali HH, et al: Anesthesiology 63:A318, 1985.
2. Gargarian MA, Basta SJ, Savarese JJ, et al: Anesthesiology 61:A291, 1984.
3. Ramsey FM, Lebowitz P, Savarese JJ, et al: Anesth Analg 59:110-116, 1980.

Title: EFFECTIVENESS OF TRIAZOLAM, DIAZEPAM AND PLACEBO AS PRE-OPERATIVE MEDICATION

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Introduction Premedication is an important aspect of preparing the patient for surgery.[1] The purpose of preoperative medication is to reduce anxiety, produce sedation and decrease post-operative recall. Benzodiazepines are frequently used because of their ability to produce these effects. It has been proposed that triazolam, a benzodiazepine with a faster onset and shorter duration of action than diazepam, may be a more useful preoperative medication. In this study we compared the anxiolytic, sedative and amnesic effectiveness of triazolam and diazepam, at 3 commonly used doses of each, against values obtained with placebo treatment and also against a theoretical "no-effect" value.

Methods The protocol was approved by our institutional review board. Patients were ASA Class I or II, between 18 and 50 years old, and with no recent or habitual use of CNS depressants. After giving informed consent, each patient was randomly assigned to receive one of 7 test medications orally: placebo; triazolam 0.125, 0.25 or 0.5 mg; or diazepam 5, 10 or 15 mg. Two hours prior to surgery a nurse clinician scored each patient's level of apprehension and sleepiness on separate 1-10 rating scales,[2] with 1 denoting the lowest possible level and 10 the highest. The test medication was given and the same behavioral evaluation repeated 60 minutes later. At that time the patient was also shown 2 different picture cards for recall testing 24 hours postoperatively.

Paired t-tests were used to determine whether differences (Δ) between 0 min and 60 min scores for apprehension and sleepiness were significantly different from zero, the theoretical no-effect value. Each medicated group's Δ apprehension and Δ sleepiness values were then compared with placebo by use of unpaired t-tests. The fraction of correctly recalled pictures was compared between groups using Fisher's exact test. P<.05 was considered statistically significant.

Results Comparisons of the anxiolytic, hypnotic and amnesic effects of triazolam, diazepam and placebo used as anesthetic premedication are summarized in the table. All groups including placebo showed decreases in anxiety after 1 hour. For 5 of the 7 groups—all except placebo and diazepam 5 mg—this anxiolytic effect was significant: i.e., anxiety was less than zero at the P<.05 level. On the other hand, only one of those 5 treatments, triazolam 0.5 mg, was significantly better than placebo at relieving anxiety. The pattern of hypnotic efficacy was exactly the same: all treatments except placebo and diazepam 5 mg significantly increased sleepiness, but only the highest dose of triazolam did better than placebo at a P<.05 level. In measurements of 24 hour recall, the placebo and no-effect values were identical: correct/total = 1. Once again, only triazolam 0.5 mg proved superior to placebo and no effect.

N	DRUG/DOSE (MG)		ΔAPPREHENSION	ΔSLEEPINESS	RECALL
11	PLACEBO		-0.5 ± 0.5	+1.2 ± 0.7	1.00
11	TRIAZOLAM	.125	-1.3 ± 0.4•	+2.2 ± 0.5•	0.95
9		.25	-1.0 ± 0.4•	+2.6 ± 0.8•	0.78
11		.5	-2.2 ± 0.4$^+$	+4.1 ± 0.7$^+$	0.68$^+$
8	DIAZEPAM	5	-1.0 ± 0.8	+0.4 ± 0.6	1.00
11		10	-1.3 ± 0.4•	+1.6 ± 0.3•	1.00
9		15	-1.4 ± 0.4•	+3.8 ± 1.1•	0.78

•P<.05 vs NO EFFECT; $^+$P>.05 vs PLACEBO AND NO EFFECT

Summary The 2 higher doses of diazepam and all 3 doses of triazolam demonstrated statistically significant anxiolytic and hypnotic effects when used as anesthetic premedication. In addition, the highest triazolam dose was better than placebo in both categories and also in the inhibition of recall. The validity of these results is strengthened by the dose-dependence of the observed effects despite the limited numbers of patients in the various groups.

Our purpose was not to compare diazepam and triazolam directly against each other on a dose-by-dose basis but rather to determine which of the drug/dose combinations commonly used is most effective in producing sedation, decreasing anxiety and preventing recall. Clearly, triazolam 0.5 mg was the most effective of those tested—in fact, the only one consistently better than placebo.

References

1. Egbert LD, Battit GE, Turndorf H, et al.: The value of the preoperative visit by an anesthetist. JAMA 185:553-555, 1963
2. Forrest WH Jr, Brown CR, Brown BW: Subjective responses to six common pre-operative medications. Anesthesiology 47:241-247, 1977

Title: INTERTUBERCULAR CERVICAL PLEXUS BLOCK: A NEW ANESTHETIC TECHNIQUE

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Introduction. The historical evolution of the cervical plexus block (CPB) has favored the lateral route, injection just superficial to the transverse processes, and caudad direction of the needle. Efforts to prevent multiple injections or to reduce total local anesthetic volume have culminated in the interscalene CPB technique. Though appealingly simple with injection of as little as 10 cc, the interscalene technique has had only an 81% success rate in our residents' hands. Reliable in the hands of our most junior residents, the intertubercular approach to CPB has evolved as a new technique requiring as little as 8 cc total local anesthetic for successful, uncomplicated blockade.

Methods. Known as Chassaignac's or the carotic tubercle, the so-called costal element of the transverse process of the sixth cervical vertebra provides rapid superficial orientation for intertubercular CPB. Independent of a patient's age, sex, or build, Chassaignac's tubercle lies about one clavicular width above a point one third of the clavicular length lateral from the sternum. Even the casual examiner easily locates this thumb-like prominence of transverse process with its attached anterior and middle scalene muscles. The description that follows assumes that the anesthesiologist is positioned at the side of a supine patient whose neck is rotated 30° to the contralateral side. The palpating hand is that closest to the patient's head. Juxtaposition of the index and middle fingers of the palpator's hand provides two finger pads for medial-to-lateral palpation of the anterior as well as posterior tubercles. The small depression sensed between the two tubercular prominences is the sulcus which transmits the sixth cervical nerve. The index finger is angled minimally caudad along the plane bisecting the intertubercular line. In order to locate the transverse process of the fifth cervical vertebra, the middle finger is applied parallel to the index finger approximately 1 to 1 1/2 cm cephalad from Chassaignac's tubercle, in the general direction of the mastoid process. When a prominence is palpated, the ring finger is applied in a similar fashion, yet another 1 to 1 1/2 cm cephalad towards the mastoid process and the prominence of the fourth cervical transverse process ascertained. Triangulation from the intertubercular baseline towards an apex at the fourth cervical transverse process constructs a plane tangential to the intervertebral sulci through which the cervical nerves emerge. Moreover, perpendiculars to this oblique plane are naturally mildly caudad in orientation, because of the increasing depth of the transverse processes as one palpates cephalad. Gradual digital pressure from the ring finger over the fourth cervical transverse process elicits mild discomfort or paresthesia in the respective dermatome. Advance warning to anxious patients who have experienced angina pectoris is appropriate before evoking a fourth cervical paresthesia. Replacing the ring finger, a short-bevel 22 gauge needle is advanced mildly caudad along a perpendicular to the triangulation plane between the tubercles of the transverse process of the fourth cervical vertebra. Following negative needle aspiration, 3 to 5 cc of local anesthetic solution is injected intertubercularly. In similar fashion, the little finger palpates 1 1/2 cm further cephalad, and 5 to 10 cc of local anesthetic is injected intertubercularly after a negative aspiration.

Results. Following informed consent, forty-two consecutive intertubercular CPBs were performed on male subjects ranging from 39 to 76 years of age. All subjects were ASA Class III and IV. Weighing from 58 to 105 kg, all patients had intertubercular landmarks easily palpable by one of our anesthesia residents. All subjects had sustained transient ischemic attacks (TIAs). Cumulative prevalence of other major morbidities in this unhealthy population included crescendo TIA in 52%; cerebrovascular accident (CVA), 48%; multiple CVAs, 5%; exertional angina pectoris (AP), 29%; rest AP, 10%; myocardial infarction, 33%; hypertension, 76%; diabetes mellitus, 33%; peripheral vascular disease, 52%; congestive heart failure, 14%; valvular heart disease, 19%; chronic obstructive pulmonary disease, 90%. Percentage of patients having cardioactive medications included 57% with beta-adrenergic blockade; 33%, calcium channel blockade; and 19% with nitrate therapy. Premedication included benzodiazepines in 86% and opiates in 10%. Intertubercular CPB was performed with 0.5% bupivacaine in 71%, 1% lidocaine in 19%, and a mixture of the two in 10%. Total local anesthetic required for intertubercular CPB ranged from 8 to 15 cc. Complete neural blockade was achieved between 10 and 20 minutes after lidocaine and between 20 and 45 minutes after bupivacaine. All 42 intertubercular CPBs performed by the 13 inexperienced residents were successful, requiring neither repeat CPB nor emergency conversions to general anesthesia. Supplemental local anesthetic was administered by the surgeon 1) at the platysma (CN VII innervation) for some of the carotid endarterectomies, 2) deep to the clavicle (periosteum) for vertebral artery reconstruction, and 3) intratracheally (CN IX and X innervation) for tracheostomy. Two patients required emergency shunting for neurological changes precipitated by cross-clamping the carotid artery. No patient sustained a perioperative MI or CVA. There were no neurologic or cardiovascular complications from the intertubercular CPBs. Hemodynamic stability was remarkable with only 14% of patients requiring vasopressor or vasodilator infusions postoperatively. All patients receiving intertubercular CPB felt that they would repeat this anesthetic for future neck procedures, and, indeed, one patient had his contralateral carotid endarterectomy performed under intertubercular CPB.

Discussion. Permitting profound blockade with as little as 8 cc total of local anesthetic volume, the intertubercular approach to cervical plexus block (CPB) avoids the risks posed by prior techniques, which include failed blockade and inadvertent arterial, epidural, or subarachnoid injection. Performed by the author and 13 previously inexperienced anesthesiology residents, 42 consecutive intertubercular cervical plexus blocks were uniformly successful and free of complications.

Title: A COMPARISON OF BUPIVACAINE AND ALKALINIZED BUPIVACAINE IN BRACHIAL PLEXUS ANESTHESIA

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Introduction. Clinically used 0.5% bupivacaine (PKa 8.1) has a low pH (4.0-6.5) to ensure water solubility. In vitro data suggests, however, that acutely raising the pH of the solution to 7.0-7.1 should enhance onset time and duration of blockade[1], without producing significant precipitation of bupivacaine crystals.

A recent clinical study of alkalinized 0.5% bupivacaine in brachial plexus anesthesia showed a reduced time to onset and prolonged duration of sensory blockade when compared to 0.5% bupivacaine with epinephrine (pH 3.9)[2]. The present clinical trial was undertaken to determine the effect of alkalinized 0.5% bupivacaine when compared to 0.5% bupivacaine plain in brachial plexus anesthesia.

Methods. The study was approved by the F.D.D. and the Human Investigation Committee at the University. Informed consent was obtained from 60 (ASA Class I-II) patients, ages 16-65, weighing 45-85 kg, scheduled for upper extremity surgery. Thirty patients were randomly assigned to each of two groups and a double-blind design was used. Patients were monitored using a standard 3 lead ECG and automatic blood pressure device. All patients were premedicated with diazepam 0.1 mg.kg^{-1} intravenously immediately prior to performing the block. A subclavian perivascular brachial plexus block was performed following localization of the plexus by paresthesae and/or with the use of a nerve stimulator.

Group I patients received 0.5% bupivacaine (Marcaine) in a dose of 3 mg.kg^{-1}. Group II patients received 0.5% bupivacaine with 0.1 ml of $NaHCO_3$ (8.4%) per 20 ml of bupivacaine (pH 7.05 - 7.15) in a dose of 3 mg.kg^{-1}. Following completion of the block, sensory and motor blockade were determined at 1,3,5,10,15,20 and 30 min., and at 30 min. intervals for 6 hours following the block. Sensory blockade was determined by pinprick using skin dermatones C_4-T_2 (1 = no response, 0 = pinprick). Motor blockade was assessed according to the following schema: 0 = no motor block, 1 = inability to abduct the shoulder or flex the elbow against resistance, 2 = inability to abduct the shoulder or flex the elbow against gravity, 3 = inability to abduct the shoulder, and flex the elbow and wrist against gravity.

The results were analyzed using T-tests and One Way ANOVA. Post-ANOVA multiple comparisons were performed using Duncan's Test. A value of $P < 0.05$ was considered significant.

Results. The two groups studied were similar in age, height, weight and sex distribution (Table I). Blood pressure and heart rate were similar in the two groups and did not change significantly during the course of the study. Of the 30 patients blocked in Group I, 23 (77%) had adequate analgesia for surgery, while in Group II, 24 (80%) had adequate analgesia. In Group I, 3 patients had a failed block, while 4 had partial analgesia, and in Group II, 3 patients had a failed block and 3 had partial analgesia. The 3 patients in each group with a failed block were eliminated with regards to analysis of onset time, time to peak effect, and regression of blockade.

Time to onset and time to peak effect of sensory and motor blockade did not differ significantly between the groups (Table II). Similarly no difference in regression of sensory or motor blockade was observed post-operatively between the groups.

No instance of central nervous system or cardiovascular toxicity was observed in either group during the study. The single complication occurring was a pneumothorax requiring chest tube drainage (incidence 1.6%).

Discussion. In contrast to previous observations[2], this study does not demonstrate any beneficial effect in alkalinization of 0.5% bupivacaine when compared to 0.5% bupivacaine plain, when a dose of 3 mg.kg^{-1} is administered. Bupivacaine 0.5% is a safe and effective agent in brachial plexus blockade providing proper technique and precautions are followed.

References.

1. Ritchie JM, Ritchie B and Greengard D. The active structures of local anesthetics. J Pharmacol Exp Ther 1965; 150:152-9.
2. Hilgier M. Alkalinization of bupivacaine for brachial plexus block. Regional Anesthesia 1985; 10:59-61.

Table I

Solution	Age (yrs.)	Height (in.)	Weight (kg.)	Male/Female Ratio
Group I n = 30	40 ± 3	68 ± 1	68 ± 1	19/11
Group II n = 30	37 ± 2	67 ± 1	69 ± 2	22/8

Values are mean ± SEM; No significant difference

Table II

Solution	Sensory blockade(min)		Motor blockade(min)	
	Onset	Peak	Onset	Peak
Group I n = 27	4.0 ± 1.2	17.7 ± 1.8	6.9 ± 1.7	18.1 ± 1.8
Group II n = 27	3.6 ± 0.9	16.3 ± 1.8	6.3 ± 1.5	15.1 ± 1.9

Values are mean ± SEM; No significant difference

This research was supported by Winthrop Laboratories, Division of Sterling Drug Ltd.

Title: REPERFUSION COAGULOPATHY DURING HUMAN LIVER TRANSPLANTATION

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Introduction. Reperfusion of a liver homograft is known to sometimes provoke a severe coagulopathy (1). Kang, et al (2) reported thrombin time prolongation (TT) in 2 of 65 adult liver recipients. This suggests, contrary to previous reports (3), that circulating antithrombin agents rarely cause this coagulopathy. In light of this controversy, this study was undertaken to examine whether circulating heparin is a significant cause of reperfusion coagulopathy (RC).

Methods. 65 liver recipients were studied (30 adults, 41 ± 7 yrs, 60 ± 13 kg; 35 children 37 ± 30 months, 12 ± 4 kg). Selection criteria, techniques of anesthetic and surgical management have been reported (4,5). The preservation solution used to flush the liver during harvesting and again before implantation contained 100 mg/l of heparin. Coagulation disorders detected prior to revascularization were corrected. Hemoglobin (Hb), hematocrit (Hct), prothrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT), platelet count (PC), and fibrinogen (Fib) were measured before, and after revascularization of the liver. "Heparin effect" was defined as prolongation of TT and the PTT, with unchanged PT, PC and Fib within 5-10 minutes of IVC unclamping. "Heparin effect" was reversed with protamine sulfate, by titration to a TT of $\leq$ 18.5 seconds.

Results. Figure 1 depicts the Hb, PT, PTT, TT, PC and Fib before and after revascularization and protamine therapy. In all 65 patients TT and PTT were significantly prolonged (39 ± 19 sec) and (55 ± 23 sec) respectively after revascularization ($p < .01$) (normal in our laboratory TT $\leq$ 18 sec, PTT $<$ 35 sec) while PC and Fib were not significantly changed. In 62 patients titration of protamine returned PTT and TT values to normal. Fibrinolysis (invitro spontaneous redissolution of the clot) was diagnosed and treated in 3 patients, in whom protamine failed to correct TT, with exchange transfusion and epsilon aminocaproic acid.

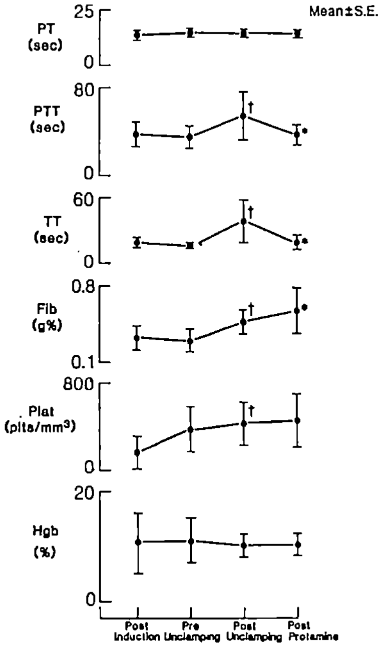
Conclusions. These data indicate that heparin sequestrated in the homograft entered the circulation when the IVC was unclamped and was responsible for the majority of cases of RC observed in our series. Protamine sulfate effectively reversed this "heparin effect". Occasionally, fibrinolysis was identified. Contrary to the report of Groth et. al (6) disseminated intravascular coagulation did not occur.

References.

1. Groth CG: Changes in coagulation. In: Starzl, TE, ed. Experience in hepatic transplantation. Philadelphia, WB Saunders, 1969, 154-175.
2. Kang YG, et. al. Intraoperative changes in blood coagulation and thromboelastographic monitoring in liver transplantation. Anaesth & Analg. 64:888-896, 1985.
3. Stremple JF, et. al.: Study of clotting factors in liver homotransplantation. Am J Surg 111:862-9, 1966.
4. Estrin JA, et. al: Anesthetic management during liver transplantation. In: Manual of vascular access, organ donation and transplantation. Eds, Simmons, Finch, Ascher, Najarian: New York Springer-Verlag, 1984, 258-291.
5. Estrin JA, et. al.: A new approach to massive transfusion during pediatric liver resection. Surgery 99(6):664-670, 1986.
6. Groth CG, et. al.: Coagulation during and after orthotopic transplantation of the human liver. Arch Surg 98:31-34, 1969.

Fig. 1

Effects of Protamine Sulfate on TT Following Revascularization of the Liver



†Significantly different from preunclamping (paired T test) $p<.01$

•Significantly different from postunclamping (paired T test) $p<.01$

Supported by Anesthesia Research Fund

Title: EVALUATION OF THE EFFECTS OF Ro 15-1788, IN CLINICAL ANESTHESIA

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Introduction - The possibility for selective antagonism of the benzodiazepine effects opened, in 1981, new perspectives in the field of experimental pharmacology and anesthesiology, as had occurred with the opioids in the past (1). Extensive "in vitro" and "in vivo" investigation, as well as the confirmation of a wide safety range for clinical use, revealed the clinical usefulness of one of these compounds, Ro 15-1788 (2). Thus, we proposed in this investigation to verify the efficacy of Ro 15-1788 during anesthesiology- surgical procedures.

Methods - Informed written consent was obtained from all patients after the protocol had been approved by the Universitys Ethics Committee. ASA I and ASA II patients were studied, divided in 2 groups of 10 subjects each: group I (control) and group II ("antagonist"). All patients were submited to elective surgeries under epidural anesthesia followed by sedation with 2 mg of flunitrazepam. If the patient woke up before the end of the surgery, aditional dose of flunitrazepam (1 mg) was administered. At the end of the surgery, CNS depression was evaluated in both groups. Group II patients received venous admiministration of Ro 15-1788, initially 0.2 mg. Soon after CNS depression was again evaluated and if the the patient was still sedated, new doses of Ro 15-1788 were injected (0.1 mg), until the patient became aware. Group I patients remained in the operating room during 60 minutes more, when the CNS depression was also once more evaluated. The antagonistic property of Ro 15-1788 was evaluated based on the following psychological testing (3): 1) cognitive - Digit Symbol Substitution Test (DSST), 2) psychomotor - Symbol Copying Test (SCT) and 3) memory - Digit Span (DS) and Auditive and Visual Memory (AVM), degree of muscular strength (MS) and the Central Nervous System (CNS) depression scale. Plasma levels of flunitrazepam 5 minutes after stopping Ro 15-1788 infusion were tentatively correlated with the dose of antagonist in group II. Statistical analysis were performed with the following tests: Fishers exact test, Mann-Whitney U-test, unpaired Students t test and the multiple correlation test.

Results - Following the administration of flunitrazepam, group I patients displayed a diminished response to all psychological tests, whereas in group II patients normal performance was maintained. Also muscular strength was reduced in all patients in group I. Evaluation of the central nervous system depression showed that all patients from both groups were deeply sedated at the end of the surgical procedure. However 60 minutes later, while group I patients were still asleep and superficially sedated, all group II patients recovered full awareness within 2 to 10 min. following the administration of 0.3 to 1.0 mg of Ro 15-1788. At this time, mean plasma levels of flunitrazepam (23.77 ηg/ml) were above those minimum sedation levels stablished in the international literature (4). No statistical significance was detected between plasma levels of flunitrazepam and the administered dose of the antagonist. No adverse effects possibly associated to Ro 15-1788 were observed.

Test	Group I		Group II	
	before drug ad.	after FNM	before drug ad.	after ant.
DSST	12.2	2.1	12.4	12.2
SCT	29.4	9.3	30.0	29.9
DS	13.4	10.8	13.5	3.4
Amnesia (%)		60.0		0
Reduced MS		100.0		0
*CNS depression scale	0	1 - 2	0	0

* CNS depression scale: 0 to 7 score, 0 = full awareness
7 = unresponsible

Discussion - We concluded that Ro 15-1788 in the dose range of 0.3 to 1.0 mg, completely reversed the following effects of flunitrazepam: sedative-hypnotic, amnestic and muscle relaxant (flunitrazepam plasma levels at this point were all elevated). No intrinsec activity due to Ro 15-1788 were observed at these dose levels (5). Thus, it seems a useful drug in the post-anesthetic recuperation of CNS depression of patients submited to the action of flunitrazepam during anesthesia.

References

1. MOHLER H & OKADA T. Benzodiazepine receptor: demonstration in the Central Nervous System. Science 1977; 198: 849-51.
2. BONETTI EP, PIERI L, CUMIN R et al. Benzodiazepine Antagonist Ro 15-1788: neurological and behavioral effects. Psychopharmacology (Berlin) 1982; 78:8-18.
3. WECHSLER D. Manual for the WECHSLER Adult Intelligence Scale-National. Formation for Educational Research, London, 1955.
4. SINCLAS E. Pharmacocinetique du flunitrazepam. Nouv Press Med 1979; 8: 2519-23.
5. DARRAGH A, LAMBE R, BOYLE CO et al. Absence of central effects in man of the benzodiazepine antagonist Ro 15-1788. Psychopharmacology 1983; 80: 192-5.

Title: THE EFFECT OF PEEP ON RIGHT VENTRICULAR DIASTOLIC PRESSURE-VOLUME RELATIONSHIPS

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Introduction. Augmented right ventricular loading with positive end-expiratory pressure (PEEP) increases right ventricular end-diastolic volume index (RVEDVI) in association with decreased right ventricular ejection fraction (RVEF). Because conventional pressure measurements of right ventricular preload do not account for alterations in right ventricular compliance or changes in juxtacardiac pressures, right ventricular end-diastolic pressure (RVEDP) may not correlate with RVEDVI (1).

Methods. In accordance with an approved Human Investigations Committee Protocol, thirty-six (n=36) post-operative ventilated patients were evaluated during a graded application of PEEP (0,5,10,15,20 cmH_2O). Intermittent positive pressure ventilation was maintained at constant tidal volume (mean=12cc/kg), F_iO_2 (mean=0.4), and respiratory rate (normocapnea). Hemodynamic measurements recorded at end-exhalation included: heart rate (HR), mean arterial pressure (MAP), RVEDP, right ventricular peak-systolic pressure (RVPSP), pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCWP). Using a rapid response thermistor (50 msec) tipped Swan-Ganz catheter, RVEF, RVEDVI, right ventricular end-systolic volume index (RVESVI) and cardiac index (CI) were calculated (2).

Analysis of data was performed using one way analysis of variance (mean±SD), multiple linear regression, and coefficient of correlation, $p < 0.05$ considered significant.

Results. PEEP induced increases in pulmonary vascular resistance index (PVRI) were directly related to increases in RVEDVI (r=0.85, $p < 0.01$) and RVESVI (r=0.78, $p<0.01$); and inversely related to changes in RVEF (r=0.98, $p< 0.01$). CI changed significantly at PEEP > 15 cm H2O while PCWP remained constant (Table I). RVEDP changed insignificantly and did not correlate with significant changes in RVEDVI which ranged from 119±15 cc/m^2 at 5 of PEEP to 152±14 cc/m^2 at 20 of PEEP (Table II) (Figure 1).

Discussion. Intermittent positive pressure ventilation with PEEP modulates right heart loading conditions and alters right ventricular diastolic pressure-volume relationships. During incremental PEEP there is no significant correlation between RVEDP and RVEDVI. Therefore, RVEDP does not accurately measure right ventricular preload during PEEP.

References.
1. Ditchey R: Volume-dependent effects of positive airway pressure on intracavitary left ventricular end-diastolic pressure. Circ 1984; 69 815-821.

2. Kay H, Afshari M, Barash P, et al: Measurement of ejection fraction by thermal dilution technique. J Surg Res 1983; 34:337-345.

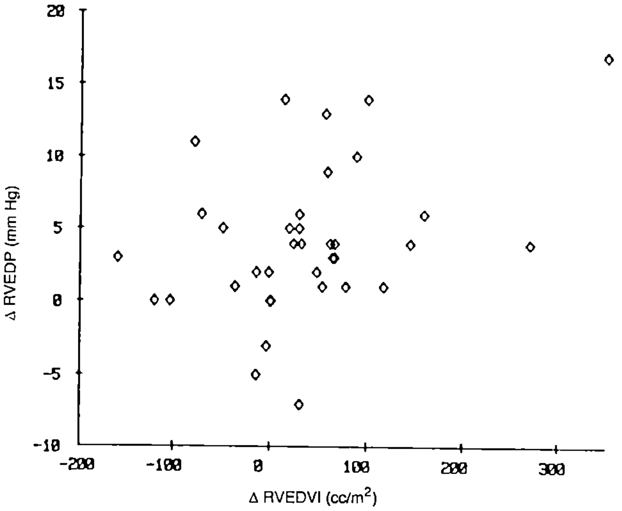
TABLE I

PEEP	RVEDP	RVEDVI	RVESVI	RVEF	PVRI	CI
cmH_2O	mmHg	cc/m^2	cc/m^2	%	$ds/cm^5/m^2$	$L/m/m^2$
0	10±5	144±17	92±16	36±14	210±40	4.3±1.8
5	7±5	119±15	78±18	36±12	240±38	4.0±1.4
10	10±4	122±12*	84±14	33±10	270±41*	3.4±1.2
15	12±5	134±12*	99±12	29±8*	298±36*	3.2±1.4
20	15±6	152±14*	120±12*	23±7*	360±38*	2.6±1.3*

TABLE II

PEEP	RVEDP	RVEDVI	COEF CORR
cmH_2O	mmHg	cc/m^2	r
0-5	-3±2	-25±15	0.354
5-10	+3±2	+3±8	0.114
10-15	+2±2	+11±6	-0.510
15-20	+3±2	+18±12	0.175

FIGURE 1



Alteration in RVEDP and RVEDVI at 0-20 cmH_2O PEEP. Note poor correlation between RVEDP and RVEDVI (r = 0.35).

Title: SINGLE BREATH END-TIDAL PCO_2 APPROXIMATES ARTERIAL PCO_2 IN INFANTS AND CHILDREN

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Introduction: End-tidal gas sampling is used to assess the adequacy of alveolar ventilation and anesthetic gas concentrations in pediatric anesthesia. However, end-tidal gas sampling is useful only if it approximates the arterial values.[1-3] To determine if end-tidal gas sampling is useful in pediatrics, end-tidal and arterial values for pCO_2 were compared in infants and children during general anesthesia.

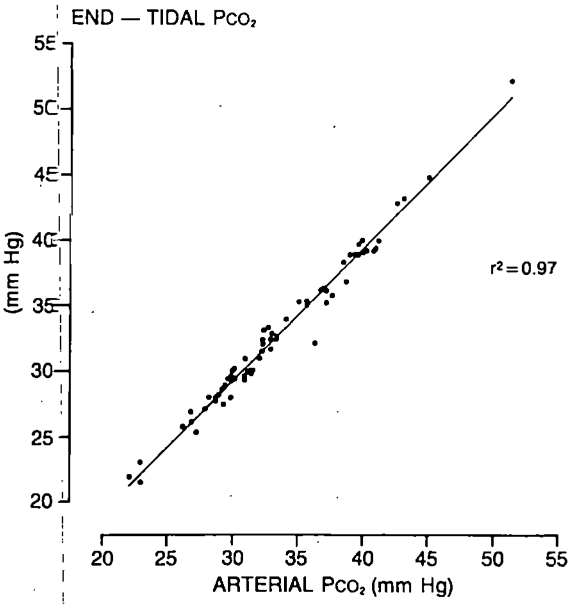
Methods: With approval from the Human Review Committee, 68 healthy infants and children scheduled for surgery requiring endotracheal intubation were studied. All infants and children were mechanically ventilated through an Ayre's t-piece. The total fresh gas flow was 2.5 to 3.0 times the alveolar ventilation. Positive end-expiratory pressure was avoided. After ventilation was controlled for 15 minutes, a single breath end-tidal gas sample was obtained as follows: a #23 gauge needle was inserted through the wall of the endotracheal tube immediately below the connector. During the next tidal volume, the fresh gas line was disconnected from the anesthetic machine at peak inspiration. During the same breath, 3-4 ml of expiratory gas were aspirated through the needle into a 5 ml plastic syringe at end-expiration. An arterial blood sample was then obtained from an in-dwelling arterial cannula or through a percutaneous arterial puncture. Both end-tidal gas and arterial blood samples were analyzed in a Corning^R blood/gas analyzer (Model 175). After inserting the end-tidal gas sample into the Corning^R analyzer, the "reset" button was pushed twice to flush the sample chamber. The blood/gas analyzer was calibrated daily with standard solutions. The end-tidal and arterial pCO_2 values were plotted on a linear scale. Least squares linear regression analysis (and the coefficient of determination, r^2) were used to correlate end-tidal and arterial pCO_2 values.

Results: The mean (± SD) age and weight for the 68 children were 6.4 ± 5.1 years and 18.4 ± 16.3 kg. The mean (± SD) end-tidal and arterial pCO_2 values were 33.6 ± 6.9 mm Hg and 33.6 ± were used to correlated very closely with the arterial pCO_2 ($r^2 = 0.97$) (Figure).

Discussion: Single breath end-tidal pCO_2 measurements accurately approximate the arterial pCO_2 values in infants and children who are mechanically ventilated with a partial rebreathing circuit. Previous studies have suggested that continuous gas sampling in pediatric patients may not accurately approximate the arterial gas tensions.[3] To minimize inaccuracies in continuous end-tidal gas sampling, we recommend the use of single breath end-tidal gas sampling for easy, accurate, and non-invasive pCO_2 monitoring in infants and children.

References:

1. Scheiber RA, Namnoum A, Sugden, et al. Accuracy of expiratory carbon dioxide measurements using the coaxial and circle breathing circuits in small subjects. J of Clin Monitoring 1985;1:149-155
2. Kaplan RF, Paulus DA. Error in sampling of exhaled gases. Anesth Analg 1983;62:955-6
3. Raemer DB, Francis D, Philip JH, et al. Variation in PCO_2 between arterial blood and peak expired gas during anesthesia. Anesth Analg 1983;62:1065-9



Title: EFFECTS OF NITROUS OXIDE ON DIRECT AND INDIRECT TESTS OF MEMORY

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Introduction. Case reports suggest that occasionally patients receiving general anesthesia recall some intraoperative events, but prospective studies have failed to elicit evidence of such "awareness." These studies used direct recall tests in which patients were asked to recall information (e.g., a list of words) read to them during surgery. Squire and his colleagues[1] have recently described several "subtle," indirect tasks which provided evidence of weak memory traces in amnesic patients that were not detected by direct memory tests. Such indirect tests might be useful in assessing memory for intraoperative events and effects of anesthetics on memory. We therefore examined several indirect tests to see if any resisted the memory-impairing effects of a subanesthetic concentration of nitrous oxide.

Methods. Thirty-two healthy young subjects (Ss), half men and the others women, participated. Informed consent and institutional approval for the study were obtained. Under double-blind conditions, half the Ss inhaled 30% nitrous oxide in oxygen (monitored by an infrared analyzer) and half inhaled 100% oxygen as a control. Tests were given before and again during gas inhalation. For each of three tasks derived from Squire's work, Ss heard a list of words twice and then were asked to write down as many of the words as they could. Following this direct recall test, one of the "subtle," indirect tests was given: (1) In Constrained Associations, for each of six categories (e.g., MILITARY TITLE), Ss were given up to 90 seconds to write eight examples of the category (e.g., GENERAL). (2) In Free Associations, for each of a series of words (e.g., KING), Ss wrote the first word that came to mind (e.g., QUEEN). (3) In Word Completion, for each of a series of three-letter word beginnings (e.g., BAL), Ss wrote a word starting with those letters (e.g., BALANCE). The words on the list which Ss had been asked to remember provided appropriate answers for half the items on each of the indirect tests. The score was derived by counting how many of these words were given and was adjusted for performance on the remaining distractor items. The score for Constrained Associations, for instance, indicated how much the likelihood of Ss giving a word as an example of a category was increased by including that word on the list of words Ss had been asked to remember. Ss returned for a second session 24 hours later. The tests described above were repeated to examine retention of the previous day's learning. No drug was administered.

Results. The effects of nitrous oxide were determined by analyses of variance. Appropriate interactions were examined for significance at the $p < .05$ level. Nitrous oxide markedly impaired recall of the words in the direct memory tests. Averaged over the three tasks, recall during gas inhalation was only 27% of the whole list for the nitrous oxide group compared to 55% for the control group. Corresponding scores before gas inhalation were 68% and 70%, respectively. In the test 24 hours later, recall of the words heard during gas inhalation on the previous day was only 9% for the nitrous oxide group vs. 23% for the controls. Corresponding scores for words heard before gas inhalation were 34% and 31%, respectively.

The indirect tests varied in their sensitivity to the impairing effect of nitrous oxide on memory. The Constrained Association test was the most resistant. Its scores were similar during gas inhalation for the nitrous oxide group and the control group (both 13%). Corresponding scores before gas inhalation were 20% and 16%, respectively. A similar absence of drug effects was seen in the test 24 hours later. The scores for words heard during gas inhalation on the previous day were 10% and 11% in the nitrous oxide and control groups, respectively. Corresponding scores for words heard before gas inhalation were 14% and 12%, respectively.

Of the other two tests, Word Completion was more reliable than Free Associations as an indirect test of memory. The overall average score for Word Completion was 14% compared to only 2% for Free Associations. Scores on Word Completion during gas inhalation were lower for the nitrous oxide group (7%) than for the control group (18%), but the groups showed a comparable difference before gas inhalation (scores of 20% and 28%, respectively). In the test 24 hours later, the scores for words heard during gas inhalation on the previous day were 5% and 15% in the nitrous oxide and control groups, respectively. Corresponding scores for words heard before gas inhalation were 8% and 15%, respectively.

Discussion. What characteristics of the Constrained Association task made it the most successful of the indirect tests? One distinguishing feature was that it was the hardest. Some Ss could not give the required number of responses in the Constrained Association task, whereas no Ss failed to give the required responses in the other indirect tests. Perhaps a difficult task in which the Ss must work hard to think of appropriate responses is more likely than an easy one to elicit words that may have been weakly activated by presentation during nitrous oxide inhalation. In any case, our results indicate that the Constrained Association test seems very promising for investigating memory during general anesthesia and surgery.

References.

1. Graf P, Shimamura AP, Squire LR: Priming across modalities and priming across category levels: Extending the domain of preserved function in amnesia. J Exp Psychol (Learn Mem Cogn) 11: 386–396, 1985

Title: CONTINUOUS INFUSION EPIDURAL 0.125% BUPIVACAINE/FENTANYL AND THE SECOND STAGE OF LABOR

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Introduction. Since 1976, and the publication of Albright's now famous editorial concerning cardiac arrest and the subsequent failures of resuscitation with bupivacaine(1), the risks and benefits of bupivacaine have been re-evaluated. The long duration of bupivacaine coupled with its high degree of protein binding and low maternal:fetal ratio however, made it difficult to abandon in obstetrical anesthesia. As a result, numerous attempts were made to modify the technique of administration of epidural analgesia utilizing lower doses, combinations with narcotics(2,3), and varied methods of administration (4), with very promising results. The effects of these techniques on labor, have not been adequately investigated. The aim of the present study was to determine the effects of a low dose bupivacaine/fentanyl combination in continuous infusion epidural, using two groups of closely matched parturients, on the second stage of labor.

Methods. The study consisted of 46 laboring parturients with no obstetrical or medical complications. Twenty three patients were given segmental epidural analgesia with bupivacaine/fentanyl (epidural group) and 23 were given no analgesia or meperidine 25-50mg intravenously (control group). Each "epidural" parturient was assigned a matched control with identical parity, labor (spontaneous vs. induced/augmented), and managed by the same obstetrician, within the same month if possible. Fetal heart rate (FHR), uterine activity, maternal heart rate and blood pressure were monitored throughout labor. All patients were premedicated with a clear antacid and prehydrated with 1-1.5L or Ringers Lactate solution. Episodes of hypotension were treated with ephedrine IV in 10mg increments if conservative methods failed. Lumbar epidural blockade was performed via the L2-3 or L3-4 interspace in the sitting position, once the patient was in active labor and the cervix was 4cm dilated. Following a test dose of 3ml bupivacaine 0.5% with epinephrine 1:200,000, 10 ml of 0.125% bupivacaine with fentanyl 50µg, was administered in two divided doses and an infusion was started with a mixture of 0.125% plain bupivacaine and fentanyl 1µg/ml. The infusion rate was 10ml/hr (hour 1), 8ml/hr (hour 2), and 6ml/hr (subsequent hours). Comparisons of the second stage durations were made between control and epidural groups separating nulliparas and multiparas. Statistical analyses of data were performed using Student's t-test for independent samples. A "p" less than 0.05 was considered statistically significant. The results and statistical interpretations are recorded in Table 2.

Results. Within each group, 10 patients were nulliparous and 13 were multiparous. The mean height and weight of the parturients is noted in Table 1. There were no statistically significant differences in the two groupss with regard to these demographics. Comparison of these closely matched groups of parturients revealed no statistically significant difference in the duration of the second stage of labor when utilizing continuous infusion bupivacaine/fentanyl lumbar epidural for analgesia during labor.

Discussion. The use of continuous infusion epidural analgesia is not a new technique. It was first described in 1963(5), although its popularity has not flourished since that time. With improvements in technology however, the technique has not only become feasable, but popular. The continuous infusion method not only eliminates the periods of inadequate pain relief for the parturient without detrimental effect on the baseline fetal heart rate, uterine activity or the neurologic and adaptive capacity scores of the neonate(6), but it also eliminates the dangerous large boluses and allows the use of lower concentrations of bupivacaine with less potential toxicity. We conclude that the bupivacaine 0.125%/fentanyl 1µg/ml continuous infusion epidural does not prolong the second stage of labor.

References.

1. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine (Editorial). Anesthesiology. 1979;51;285.
2. Justins DM, Francis D, Houlton PG, et al. A controlled trial of extradural fentanyl in labour. Br. J. Anaesthesia. 1982;54;409.
3. Vella LM, Willatts DG, Knott C, et al. Epidural fentanyl in labour: An evaluation of the systemic contribution to analgesia. Anaesthesia. 1985;40;741.
4. Li DF, Rees GA, Rosen M. Continuous extradural infusion of 0.0625% or 0.125% bupivacaine for pain relief in the primigravid labour. Br. J. Anaesthesia. 1985;57;264.
5. Scott DB, Walker LR. Administration of continuous epidural analgesia. Anaesthesia. 1963;18;82.
6. Abboud TK, Afrasiabi A, Sarkis F, et al. Continuous infusion epidural analgesia in parturients receiving bupivacaine, chloroprocaine, or lidocaine-maternal, fetal, and neonatal effects. Anesthesia and Analgesia. 1984;63;421.

Table 1. Patient demographics

	Weight (lbs.) Mean ± SD	Height (in.) Mean ± SD
NULLIPARAS		
Epidural	158.70 ± 35.78	64.80 ± 3.01
Control	180.10 ± 21.17	64.85 ± 3.32
MULTIPARAS		
Epidural	167.77 ± 26.78	64.77 ± 2.74
Control	155.00 ± 36.32	62.73 ± 1.94

Table 2. Duration of the 2nd Stage of Labor (minutes)

NULLIPARAS		
Epidural	75.30 ± 44.32	p=0.829
Control	71.70 ± 50.32	
MULTIPARAS		
Epidural	43.46 ± 29.56	p=0.871
Control	45.46 ± 44.83	

Values are Mean ± SD

Title: PULMONARY FUNCTION WITH POSITIONAL CHANGE AND DURING BUPIVACAINE VS. PONTOCAINE SPINAL IN OBSTETRICS

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Introduction. The effects of positional changes or various spinal anesthetic agents on diaphragmatic respiratory function in the pregnant patient has not been studied extensively. As the pregnancy progresses, abdominal breathing decreases while thoracic breathing increases (1). Intercostal muscle activity however, is susceptable to blockade during spinal anesthesia as the level of motor blockade rises. This study was undertaken to investigate the effects of a positional change, and the effects of two different spinal anesthetics, pontocaine and bupivacaine, on respiratory function in the parturient.

Methods. Following approval by the Medical Research Committee, thirty ASA Class I or II pregnant females at term, free of respiratory illness, were studied prior to and during elective cesarean section. The Forced Vital Capacity (FVC) and Negative Inspiratory Force (NIF) were measured in all parturients (n=30) while sitting erect and repeated with the patient supine with right uterine displacement (RUD). After oral antacid premedication and appropriate prehydration, the participants were then assigned to one of two groups by the anesthesiologist performing the spinal. Group A (n=15) received Bupivacaine 0.75%/Dextrose 8.25%, while Group B (n=15) reveived Pontocaine 1%/ Dextrose 10% with doses appropriate for a T4 sensory level. Spinal anesthesia was administered in the lateral position, at L2-3 or L3-4 and the patients were immediately returned to the supine position with RUD and oxygen was administered by mask. After the sensory level was measured by pinprick, FVC and NIF measurements were repeated by a respiratory therapist and anesthesiologist, unaware of the agent used. Statistical analyses were performed on all data using Student's "t" test, paired and unpaired where appropriate, with "p" less than 0.05 significant.

Results. There was no significant difference between the two groups with respect to height, weight Body Mass Index (BMI), or sensory level of spinal anesthesia. Comparing FVC and NIF (Table 1), there is no significant difference between the sitting and supine positions. The second part of the study compares the supine unanesthetized to the supine anesthetized parturient. Again, there is no significant difference (Table 2) in either group, before or after administration of either of the spinal anesthetic agents. Likewise there was no significant difference (Table 2) when comparing bupivacaine to pontocaine. The post spinal values for each agent were compared to pre spinal values and a percentage of the control was calculated. These percentages were compared for both agents and again showed no significant difference between the two agents.

Discussion. Despite the theory that the uterus may impinge upon the diaphragm, especially while the parturient is sitting, our results indicate that there is no statistically significant impairment of respiration, sitting opposed to supine. The purpose of the second part of the study was to evaluate, using two distinctly different agents, what assist if any, the intercostals provide. Our results demonstrate no significant impairment of respiration while sitting, supine, or anesthetized, despite the agent. It appears therefore that the contribution to respiration by the intercostals in the parturient is no more significant than in the nonpregnant patient. If respiratory insufficiency occurs, it is probably a result of inadequate perfusion of the respiratory control centers in the medulla, secondary to hypotension (2). The parturient appears to be no more susceptable to a "motor blockade" respiratory insufficiency than the surgical patient.

References.
1. Shnider SM, Levinson G. Obstetric Anesthesia. In Miller RD, ed. Anesthetis, Vol 3, 2nd Ed. New York, Churchill Livingstone, 1986; 1681-1728.
2. Greene NM. Physiology of Spinal Anesthesia. 3rd Ed. Baltimore, Williams & Wilkins, 1981; 147-168.

Table 1. Measured Values of Sitting vs. Supine

	Sitting	Supine	p
FVC	2.834 ± 0.108	2.740 ± 0.100	0.5348
NIF	63.167 ± 5.35	63.600 ± 5.14	0.9084

Values are MEAN ± standard error of mean (SEM)
FVC values are Liters, NIF values are cm H_2O

Table 2. Comparison pre/post spinal (agent specific)

		Pontocaine (n=15)	Bupivacaine (n=15)
FVC	Prespinal	2.698 ± 0.115	2.783 ± 0.167
	Postspinal	2.510 ± 0.142	2.760 ± 0.138
p		0.3156	0.8810
NIF	Prespinal	54.33 + 5.55	72.86 + 8.17
	Postspinal	53.70 + 5.32	69.03 + 7.92
p		0.8942	0.7352
Sensory T= p= 0.8063		4.13 ± 0.13	4.20 ± 0.26
Sp% Control (FVC) p= 0.1315		92.88 ± 3.18	101.26 ± 4.41
Sp% Control (NIF) p= 0.5200		99.40 ± 3.56	95.60 ± 4.50

Values are MEAN ± standard error of mean (SEM)
FVC values are Liters, NIF values are cm H_2O

Title: DOES DOPAMINE IMPROVE FUNCTION OF THE TRANSPLANTED KIDNEY?

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Introduction. In normal native kidneys dopamine (1-5μg/kg/min) increases renal plasma flow (by approximately 57%), glomerular filtration rate (GFR, by 16%), and urine output (UO).[1] A newly transplanted kidney however has been subjected to surgical denervation, trauma, hypothermia, ischemia, and large doses of lasix and mannitol. Thus it may be less responsive to dopamine than a native kidney. To determine this we studied the intraoperative effects of dopamine on UO and GFR after revascularization of transplanted kidneys. In these studies GFR was estimated by using the clearance of meglumine iothalamate (MI), a substance that like inulin is filtered by[2] the kidney but neither secreted nor reabsorbed.

Methods. After institutional approval and informed consent we studied 14 adult patients with end stage renal disease undergoing renal transplantation from related donors. After premedication with halcion (0.125-0.25 mg po) anesthesia was induced with thiopental (2-4 mg/kg) and maintained with N20 60% in 02 and isoflurane (1% end-tidal concentration) as measured by mass spectrometry. Following induction of anesthesia a central venous pressure line was placed in the control patients (group 1, n=8) and a pulmonary artery catheter was placed in the patients who were to receive dopamine (group 2, n=6). Both groups of patients received IV fluid to maintain the CVP at pre-revascularization levels. Prior to revascularization MI was administered by IV bolus followed by an infusion in order to achieve an approximate plasma iodine concentration of 0.15%. All patients also received lasix (80mg) and mannitol (12.5g) prior to the release of the vascular clamps. After ureteral implantation and bladder closure blood and urine samples were collected every 5 minutes for 45 minutes. GFR was determined for each period by measuring iodine concentration in plasma and urine by fluorescent excitation analysis. In group 1 samples were collected as described above. In group 2 blood and urine collections were begun at the same time following revascularization as in group 1. After 15 min of sampling, dopamine was infused at a rate sufficient to maintain the cardiac output (CO) at 10% above the pre-revascularization level and sampling was continued for an additional 30 min. For each collection period mean arterial pressure (MAP, Dinamap), heart rate (HR), CO, and UO were measured and systemic vascular resistance (SVR) and GFR were calculated. Data were compared using Student's t test for unpaired samples. A value of P<0.05 was considered statisically significant.

Results. UO and GFR did not differ between the two groups at any time during the collections (Table 1, Table 2, X±SE). MAP remained stable in group 1 throughout the collections (Table 1). During the infusion of dopamine, CO and MAP increased in group 2 without a change in SVR (Table 3, X±SE).

TABLE 1: UO, GFR, and MAP (Group 1)

Time (min)	0-15	15-30	30-45
UO (ml/min)	19.4±2.9	19.1±2.8	14.3±2.2
GFR (ml/min)	37.9±3.6	37.9±3.3	32.3±2.8
MAP (mm Hg)	82.4±1.8	83.7±2.5	79.1±2.1

TABLE 2: Effect of Dopamine on UO and GFR (Group 2)

	No Dopamine	Dopamine	
Time (min)	0-15	15-30	30-45
UO (ml/min)	13.1±1.6	17.6±3.1	16.8±2.1
GFR (ml/min)	29.7±2.8	35.9±3.9	35.2±2.6

TABLE 3: Cardiovascular Effects of Dopamine (Group 2)

	No Dopamine	Dopamine	
Time (min)	0-15	15-30	30-45
MAP (mm Hg)	99.8±3.6	110±4.5	110±2.9
HR (bpm)	76±3.6	80±2.8	73±3.8
CO (l/min)	6.7±0.7	7.8±0.7	7.4±0.6
SVR	1220±145	1140±114	1240±104

*SVR was measured in dyne-sec/cm^5.

Discussion. In spite of trauma, hypothermia, and ischemia the GFR for a newly transplanted kidney (related donor) was approximately 90% (40 ml/min) of that for a single native kidney. Infusion of dopamine (1-5μg/kg/min) did not significantly increase the GFR or UO of the transplanted kidney. The CO and MAP increases suggest that more than a dopaminergic dose was administered, whereas the stable SVR suggests absence of alpha receptor stimulation. The lack of dopamine effect could be explained in several ways: 1) Dopaminergic receptor responsiveness was depressed by the ischemia, trauma, and hypothermia. 2) A maximal response had already been achieved in the kidney by the lasix and mannitol. We conclude that dopamine may not be useful, intraoperatively, to improve GFR and UO in the transplanted kidney.

References. 1. Goldberg, L., Pharmacolcgical Reviews, 24:1, 1972.
2. Guesry, P. et. al., Clinical Nephrology, 3:134, 19[illegible].

TITLE: "KIDDIE CAUDALS": EXPERIENCE WITH 1154 CONSECUTIVE CASES WITHOUT COMPLICATIONS

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INTRODUCTION: In 1982 McGown[1] reported the largest single series of 500 consecutive caudal blocks used to provide operative anesthesia and postoperative analgesia in children. His series, however, reported several serious complications. There were four perioperative deaths and seven cardiac arrests, four of which were directly attributed to toxic reactions to local anesthetics.

The purpose of this study was to document the safety of caudal blocks used in conjunction with light general anesthesia when used to provide adjunct intraoperative anesthesia and/or postoperative pain relief for surgical procedures below the diaphragm in infants and children.

METHODS: The standard procedure for block placement at our institution was followed. Informed consent was obtained from parents prior to surgery. All blocks were performed following the induction of general anesthesia. However, based on the preference of the anesthesiologist and the anticipated duration of surgery, the blocks were either placed prior to the onset of surgery or at its completion. Bupivacaine hydrochloride solution was used in all cases. The total dose of bupivacaine was limited to 3 mg/kg. Frequent aspiration prior to and during the injection of all local anesthetic solutions was used to reduce the risk of inadvertent intravascular and subarachnoid injections. Epinephrine was not routinely used and test dosing was not employed. For sacral and perineal procedures, a dose of 1 ml/yr of age was used. For lower abdominal procedures, a volume of 0.056 x wt in kilograms x 12 (segments) was selected. All caudal blocks performed for surgical procedures between 1 July 1982 and 30 December 1985 were analyzed. The study data were obtained from two sources: 1) Regional Anesthesia Data Sheets (RADS) that had been prospectively completed by the attending anesthesiologist or resident who performed the block, and (2) Anesthesia records of all patients who underwent surgery below the diaphragm were reviewed to identify children who received a caudal block, but whose RADS were unavailable. The following data base was assembled for each patient: age, type of surgery performed, whether the block was placed prior to or after completion of surgery, the percentage of caudal blocks used in ambulatory surgery patients, and the incidence of perioperative block complications. The data base also included results of a telephone survey of 130 randomly selected parents that was performed one to several months following surgery. Questions included their satisfaction with their child's anesthetic experience, the duration of their child's postoperative analgesia, and whether their child developed any latent complications which could be attributed to the anesthetic.

RESULTS: A total of 1154 patients, ranging in age from one month to 18 years, received one or more caudal blocks during the period of the study. Twenty-four percent of the children were under one year of age and 43% were less than two. Sixty percent of the patients had their blocks placed prior to the start of surgery, 35% at its completion, and 5% had two blocks, one at the beginning and one at the end of surgery in order to provide a longer period of postoperative analgesia. Sixty-five percent of the blocks were performed on ambulatory surgical patients. Caudal blocks were used most frequently in conjunction with genitourinary procedures (81%) that included: orchidopexy, circumcision, hydrocelectomy, and hypospadias repair. Ten percent were utilized for inguinal hernia repair, 6% for lower extremity orthopedic surgery, and 3% for other operative procedures performed below the diaphragm.

There was one case of inadvertent dural puncture in a 4 year old child. This was rapidly detected during aspiration and bupivacaine was not injected. The needle was repositioned and the block was completed without difficulty. No intravascular injections, toxic drug reactions, hypotension or other perioperative complications were detected in any patient in this series.

Telephone follow-up failed to reveal any latent anesthesia related complications. The parental survey revealed that 58% of the patients were comfortable for greater than 2 hours after surgery, with 37% of these comfortable for more than 6 hours. Postoperative pain medication was not necessary in 33% of the patients. Ninety-three percent of the parents expressed satisfaction with their child's anesthetic experience.

DISCUSSION: Recent studies have shown that children who had caudal blocks placed after the induction of general anesthesia had less postoperative agitation and decreased narcotic a requirement during recovery than did matched controls who had only general anesthesia. We have shown that "kiddie caudals" can be safely employed to provide adjunct operative anesthesia and postoperative analgesia in infants and children and believe its practical advantages outweigh the theoretical risks of combining two anesthetic techniques. In contrast to McGown's study, no toxic reactions or complications were encountered in any of our 1154 caudal blocks. Several factors may have influenced our more favorable results: better patient selection, smaller dosages of local anesthetics, and our combining the caudal blocks with a light general anesthetic. The key to the safety of the procedure is knowledge of the anatomy in children and how it differs from adults, meticulous attention to detail in site selection and preparation, and careful aspiration to be certain that neither a vessel nor the subarachnoid space has been entered.

REFERENCES

1. McGown RG. Caudal analgesia in children: Five hundred cases for procedures below the diaphragm. Anaesthesia 37:806-818, 1982.

TITLE: CAUDAL ANALGESIA IN PEDIATRIC OUTPATIENT SURGERY: A COMPARISON OF THREE DIFFERENT BUPIVACAINE CONCENTRATIONS

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INTRODUCTION: Prior studies[1,2] have demonstrated that regional blocks performed with 0.25% bupivacaine hydrochloride provide effective postoperative pain relief 80-86% of the time following either circumcision or orchidopexy in children. The current study examines whether caudal blocks performed with more concentrated bupivacaine solutions, i.e., 0.30% and 0.375%, would result in a greater rate of block success and produce more effective postoperative analgesia without delaying discharge from the hospital.

METHODS: This prospective study was approved by the Institutional Review Board, and informed consent was obtained in every case. Fifty-three ASA I or II children, ages 4-11 years, undergoing ambulatory circumcision, orchidopexy, hydrocelotomy and inguinal hernia repair were randomly assigned to one of three groups. Following induction with either intravenous thiamylal or with N_2O, O_2 and halothane, but prior to the start of surgery, children in groups 1,2 and 3 received a caudal block using bupivacaine hydrochloride in concentrations of 0.25%, 0.30%, or 0.375% respectively. Epinephrine 1:200,000 was added to all solutions. The caudal blocks were used to provide adjunct intraoperative anesthesia and postoperative analgesia. The dose of bupivacaine was calculated to provide 12-segment analgesia by using a volume of 0.056 mg/kg X (12) segments as described by Takasaki[3] and was administered in a randomized, double blind fashion. Anesthesia was maintained throughout surgery with 70% N_2O, O_2 and halothane delivered by mask. Since all caudal blocks were placed after the induction of general anesthesia, the following criterion was used to evaluate block function, i.e., if the inspired halothane concentration could be reduced to 0.5% or less 20 to 30 minutes after the onset of surgery, the caudal block was assumed to be functional. If it could not be reduced, the block was repeated by an attending anesthesiologist at the end of surgery with 0.25% bupivacaine containing epinephrine 1:200,000. In the recovery room and short stay unit, a trained observer evaluated the intensity of the patient's postoperative pain and discomfort at predetermined intervals until they met all standard criteria for discharge from the hospital. Pain and/or discomfort were equated with posturing, agitation, crying, blood pressure elevation, and verbalization on a scale of 0-2 for each of the five categories. In addition, children who were 7 to 11 years of age performed a self-assessment of their level of pain and discomfort using a 0-10 linear analogue pain scale. Fentanyl 1 ug/kg IV was given to all children scoring 6 or more points on either scale. The time required to meet discharge criteria was noted, and differences among the three groups were compared using analysis of variance techniques.

RESULTS: A total of 53 blocks were performed. Forty-eight patients had satisfactory adjunct operative anesthesia and postoperative analgesia, regardless of the bupivacaine concentration used. Five blocks (9.5%) failed to meet the criterion for satisfactory intraoperative analgesia. The block failures were equally dispersed among the three bupivacaine concentrations, (two each in the 0.25% and 0.30% groups, and one in the 0.375% group). The blocks were repeated in these five children at the completion of surgery, and they were eliminated from the discharge time analysis. None of the children required supplemental postoperative analgesia. Discharge times were 181 + 20, 185 + 22 and 226 + 29 minutes for children who received 0.25%, 0.30% and 0.375% bupivacaine, respectively (Table). These differences were not statistically significant ($p > 0.3$).

DISCHARGE TIME*

Bupivacaine Concentration (n)	Mean Time in Minutes	Standard Error of the Mean
0.25% (17)	181	± 20
0.30% (14)	185	± 22
0.375% (17)	226	± 29

not significant $p > .32$
***five repeated caudal blocks excluded from analysis**

DISCUSSION: All of the children had effective postoperative analgesia. Bupivacaine solutions of 0.30% and 0.375% concentration did not appear to offer any advantage when performing caudal blocks in these patients. Five of the caudal blocks (9.5%) failed to provide adequate adjunct operative anesthesia. Since these failures were corrected when an attending anesthesiologist repeated the caudal injections at the completion of surgery, they were most likely due to either poor technique or inadequate volume. However, one cannot rule out the possibility that these five blocks may have provided effective postoperative analgesia without the need for repeating them with 0.25% bupivacaine at the completion of surgery. In summary, it is concluded that caudal blocks performed with 0.25% bupivacaine containing epinephrine 1:200,000 produce effective postoperative analgesia in children undergoing either inguinal or penile procedures. There does not appear to be any advantage to using more concentrated solutions such as 0.30% and 0.375% bupivacaine.

REFERENCES

1. McGown RG: Caudal analgesia in children: Five hundred cases for procedures below the diaphragm. Anaesthesia 37:806-818, 1982.

2. Hannallah RS, Broadman LM, Belman AB, et al: Control of post-orchidopexy pain in pediatric outpatients: Comparison of two regional techniques. Anesthesiology 61(3A):A429, 1984.

3. Takasaki M, Dohi S, Kawabata Y and Takahashi T: Dosage of lidocaine for caudal anesthesia in infants and children. Anesthesia 47:527-529, 1977.

TITLE: REGIONAL VS. GENERAL ANESTHESIA: A SURVEY OF ANESTHESIOLOGISTS' PERSONAL PREFERENCE

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INTRODUCTION: In 1973, Katz[1] asked all physicians who listed anesthesiology as their specialty, "If you were a surgical patient, which anesthetic technique and agent would you prefer for yourself?" More than two-thirds (68%) of those responding expressed a preference for regional anesthesia. Katz was concerned, however, that regional anesthesia might become a lost art because proper training in this technique seemed lacking in many residency training programs at that time.

We conducted this study to determine if a regional anesthetic was still preferred by a majority of anesthesiologists, and whether certain demographic variables influenced their choice.

METHOD: Four hundred forty-six anesthesiologists were chosen at random from the directories for the American Society of Anesthesiologists (ASA, n = 302) and the American Society of Regional Anesthesia (ASRA, n = 144). Each was sent a questionnaire describing two scenarios. In Scenario "A," the anesthesiologist sustains an open fracture of the tibia immediately after eating lunch, with an Open Reduction, Internal Fixation (ORIF) scheduled in 2-4 hours. Scenario "B" occurs 6 months later, when the anesthesiologist is to undergo elective surgery for removal of the tibial plate. In each scenario, the anesthesiologist has no other medical problems (ASA Classification I or IE). An anesthesiologist capable of performing all types of lower extremity regional anesthetics is available to perform a regional block or to administer a general anesthetic. Within each scenario, the following questions were asked:

1. I would:
   a. strongly prefer a general anesthetic
   b. prefer a general anesthetic
   c. have no preference
   d. prefer a regional anesthetic
   e. strongly prefer a regional anesthetic
2. If a regional anesthetic is preferred, what type of block do you desire?
   a. subarachnoid
   b. epidural
   c. caudal
   d. sciatic and femoral-inguinal-paravascular (3-in-1)

Demographic data requested included: age, the year in which residency training in anesthesia was completed, membership in ASRA, and the percentage of their practice involving regional anesthesia. The geographical location of each response was obtained by examining the zip code of the returned postmark. All replies were confidential and anonymous.

RESULTS: Two hundred fourteen replies were received from 446 questionnaires (48%). As shown in the table, the anesthesiologists in both scenarios strongly preferred a regional anesthetic. Preference for a regional anesthetic was greater in Scenario "A" (emergency surgery) than in Scenario "B" (elective surgery). All differences were significant at the $p< 0.001$ level.

Preferred Technique	EMERGENCY "A" n	(%)	ELECTIVE "B" n	(%)
REGIONAL	196	(91.6)*†	158	(73.9)*•
GENERAL	11	(5.1)†	39	(18.2)•
NO PREFERENCE	7	(3.3)	17	(7.9)

*$p < 0.001$ (Scenario "A" vs. "B") Regional

†$p < 0.001$ (Regional vs. General) Scenario "A"

•$p < 0.001$ (Regional vs. General) Scenario "B"

Sixty-five percent of the anesthesiologists who desired a regional technique for their emergency surgery elected to have a spinal anesthetic and 30% an epidural. The 3-in-1 block was only requested by 4% of those polled for Scenario "A" and 7% for Scenario "B". Only 1% desired a caudal block in both settings. Spinal anesthesia was less popular in the elective setting (56%) than in the emergency situation. Many of the 36% who desired an epidural block for their elective repair, Scenario "B", indicated by write-in that they chose this modality, so they could have epidural narcotics for postoperative pain relief.

No differences were seen when anesthetic preferences were associated with membership in ASRA, the number of years in practice (greater than or less than 15 years), geographical location, or the frequency with which the respondents performed regional blocks in their own practice settings.

Anesthesiologists less than 40 years of age strongly preferred a regional technique for emergency surgery, more frequently than did older anesthesiologists, ($p< 0.02$).

DISCUSSION: In Katz's 1973 study, the anesthesiologists' overall preference rate for regional anesthesia was 68%, compared to a 74% rate for non-emergency surgery in our study. While these differences were not statistically significant, our study indicates that anesthesiologists still would prefer regional anesthesia for their own extremity surgery. Emergency surgery increases the likelihood that a regional anesthetic will be chosen. Anesthesiologists less than 40 years of age preferred a regional anesthetic for emergency surgery more strongly than did older anesthesiologists. This may imply that the inherent safety, convenience, and postoperative analgesia associated with regional techniques are being appropriately stressed in today's residency training programs.

REFERENCES

1. Katz, J: A Survey of Anesthetic Choice Among Anesthesiologists. Anesth Analg 52(3): 373-5, 1973.

Title: NEUROLYTIC CELIAC PLEXUS BLOCK FOR PANCREATIC CANCER: EFFECT OF RADIOGRAPHIC NEEDLE GUIDANCE AND METASTASES

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Introduction: Neurolytic celiac plexus block (NCPB) has been established as useful in alleviating pain due to intra-abdominal malignancy. Investigators have documented NCPB provides significant abdominal pain relief from pancreatic carcinoma in 70% to 94% of patients, but results in neurologic complications in from 1% to 12% of patients.[1,2] As a result, investigators have suggested NCPB should be performed with radiographic needle guidance.[3,4] It has also been suggested that the efficacy of NCPB is decreased when pancreatic metastases are present. To determine whether the quality and length of pain relief or complication rate varied with use of radiographic assisted needle placement or presence of metastases, we analyzed NCPBs performed on 136 patients with pancreatic cancer.

Methods: After approval of the Institutional Review Committee, we reviewed the medical records of all patients with pancreatic cancer receiving alcohol NCPB, from the years 1978 to 1985. The variables recorded included: quality and length of pain relief, complications, method of radiographic needle guidance, and presence of metastases. Quality of block was graded poor or good according to review of patients' post-block pain relief, analgesic requirements, and primary physicians' records. Length of pain relief following the first NCPB was recorded in total weeks and as a percentage of a patient's survival. Complications were assessed from both hospital and primary physicians' records.

Results: Records were available on 136 pancreatic cancer patients who underwent NCPB with 50 ml of 50% alcohol via bilateral needles. First block pain relief was judged good in 116 patients (85%) and poor in 20 (15%). Repeat NCPBs were performed in 18 (13%) of the cases. Pancreatic metastases did not affect quality of pain relief. (Table 1) Use of radiographic guidance did not improve the quality of pain relief. (Table 2) When good first block pain relief was achieved, it lasted through the patient's remaining life in 75% of cases, and for more than 50% of survival time in another 12.5% of cases. Patients lived from one to 364 weeks (mean=26.6 ± 6.2 wks SEM; median=12 wks) following the blocks. There were no neurologic complications. A pneumothorax occurred in two patients (1.3% incidence); one with (plain film) and one without radiographic needle guidance. No medicolegal claim resulted from these NCPBs.

Discussion: No neurologic complications occurred during 154 NCPBs in 136 patients, suggesting that routine use of radiographic needle guidance at our institution may be unwarranted. These data also document that radiographic needle guidance did not improve the quality of NCPB pain relief, or decrease the incidence of pneumothorax. Presence of pancreatic metastases did not adversely affect the quality of pain relief with NCPB. In spite of this, individuals performing this technique infrequently or desiring medicolegal documentation of needle placement may find radiographic confirmation useful.

TABLE 1: QUALITY OF BLOCK AND PRESENCE OF METASTASES

Block quality	No mets	+mets
Poor	15	5
Good	87	28
Total	102	33

(Fisher's Exact p=0.57)

TABLE 2: QUALITY OF BLOCK ACCORDING TO USE OF RADIOGRAPHIC GUIDANCE

	Radiographic guidance		
Block quality	None (N)	Plain film (P)	CT scan (C)
Poor	4	12	3
Good	54	53	8
Total	58	65	11

(Fisher's Exact for multiple comparisons p=0.05, 0.7[illegible] 0.37 for N:P, N:C, P:C, respectively)

References.
1. Black A, Dwyer B: Coeliac plexus block. Anesth Intens Care 1:315-318, 1973.
2. Thompson GE, Moore DC, Bridenbaugh LD, Artin RY: Abdominal pain and alcohol celiac plexus nerve block. Anesth Analg 56:1-5, 1977.
3. Singler RC: An improved technique for alcohol neurolysis of the celiac plexus. Anesthesiology 56:137-141, 1982.
4. Hegedus V: Relief of pancreatic pain by radiography-guided block. AJR 133:1101-1103, 1979.

TITLE: PATIENT-CONTROLLED ANALGESIA (PCA) FOR POSTOPERATIVE PAIN CONTROL IN ADOLESCENTS

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INTRODUCTION: Patient-controlled analgesia (PCA) has been used for some time in adult patients to treat a variety of painful conditions, including postoperative pain.[1,2] Excellent results have been obtained when PCA has been compared to more traditional methods of administering narcotic analgesics in adults.[2] To our knowledge PCA has not been previously used to control postoperative pain in children, in whom IM narcotic injection, either timed or p.r.n., remains the most commonly used method of providing analgesia. This is a preliminary report of our experience with the use of PCA in a group of adolescent patients, the youngest of whom was 11 years old.

METHODS: This prospective study was approved by the Institutional Review Board, and informed consent was obtained in every case. Ten patients, aged 11-19 years, used PCA to manage their postoperative pain after the following surgical procedures: thoracotomy, colostomy, colostomy closure, Harrington rod placement, rectal pull-through, pleural stripping and vein stripping. All patients had either received p.r.n. narcotics for pain relief following a prior surgical procedure or had been receiving IM narcotics p.r.n. during their current hospitalization prior to being switched to PCA. The primary nurse, parents, and patients all were taught how to use the PCA instrument (Abbott Lifecare), which allows patients to control their pain by simply pushing a bedside switch which engages a pump that administers a small pre-determined dose of intravenous narcotic. The parents were admonished that they were never to depress the PCA button; this was to be done only by the child. The goals of optimal pain management were discussed during the training session. These were: to provide adequate pain relief, to minimize side effects such as respiratory depression and drowsiness, to promote maximum activity, and to allow the patient to be in charge of his or her own pain management. Patients who had moderate or severe pain at the time PCA was initiated were given a loading dose of morphine sulfate until they reported that they were pain-free. Data collection was begun after the administration of these loading doses. PCA maintenance doses of morphine sulfate were initially set at 0.02 mg/kg, with a lockout interval of 15 minutes. (The lockout interval is a period during which further depression of the PCA button fails to activate the pump.) Maintenance doses and lockout intervals were adjusted during the study in order to obtain maximum analgesia with minimum side-effects (drowsiness).

At the completion of treatment, each patient was asked which mode of postoperative pain control they preferred, p.r.n. or PCA narcotic administration. In addition, the patient's primary nurse was asked to evaluate the patient's level of alertness and discomfort prior to and during PCA and to offer additional observations concerning PCA as compared with traditional methods of narcotic administration.

RESULTS: There were no complications associated with PCA. Nine patients were able to use PCA effectively. The remaining patient displayed some anxiety concerning self-administration of narcotics and PCA was discontinued (Table). The four patients who had received conventional p.r.n. therapy for previous surgery all reported that PCA was more satisfactory. The five patients referred for PCA treatment because of the failure of conventional therapy to control their pain during their current hospitalization also reported that PCA was superior to p.r.n. therapy. Four of the ten patients utilized PCA for 6-19 days to provide analgesia prior to painful procedures such as wound debridement, dressing changes, and chest physical therapy.

Nurses reported that the patients were more alert and had less pain following PCA than with conventional therapy. They unanimously preferred PCA to the p.r.n. method of narcotic administration and noted that PCA required less nursing time. PCA was also enthusiastically accepted by parents.

PCA MORPHINE FOR POSTOPERATIVE PAIN CONTROL IN ADOLESCENTS

Patient's Age	Procedure	Dosage (mg) PCA Administration (1)	Dosage (mg/kg/24 hrs)
12	Harrington Rod Placement	1.0	0.59
13	Thoracotomy	1.2	0.55
18	Rectal Pull-Through	1.5	0.34 (2)
19	Thoracotomy	1.5	0.60
12	Colostomy	1.0	0.60
19	Vein Stripping	1.5	0.29
18	Colostomy	1.2	0.70
15	Colostomy Closure	1.5	0.45
15	Pectus Repair	1.2	0.56
11	Splenectomy	0.8	0.45

(1) Lockout interval for each patient - 15 minutes.
(2) PCA discontinued because of inability to understand instructions.

DISCUSSION: This series demonstrates that adolescents as young as 11 years of age can safely and efficaciously use PCA. All patients in this series obtained excellent analgesia with very minimal sedation. No adverse side effects or complications were detected. PCA is suitable for the management of postoperative pain in adolescents who undergo surgical procedures that require extensive or extended narcotic analgesia. Controlled studies are currently underway to compare the efficacy and safety of PCA with traditional methods of pain control in younger children.

REFERENCES:

1. Bennett RL, Batenhorst RL, Bivens BA, et al: Patient-Controlled Analgesia: A New Concept of Post-operative Pain Relief. Ann Surg 195:700-704, 1982.

2. Seckzer PH: Studies in Pain With the Analgesic-Demand System. Anesth Analg 50:1-10, 1971.

TITLE: THE EFFECT OF AGE THE ADRENERGIC RESPONSE TO ENDOTRACHEAL INTUBATION

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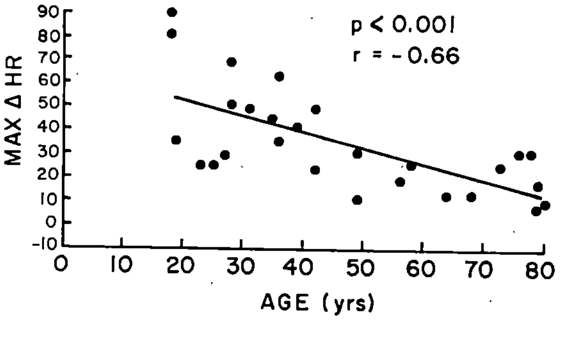
Introduction. The adrenergic response to laryngoscopy and intubation is accompanied by hypertension, tachycardia, and an increase in plasma catecholamine concentrations, while aging is associated with profound cardiovascular changes such as diminished baroreceptor function and reduced β-adrenergic sensitivity. The purpose of the present study, therefore, was to determine the effect of aging on the hemodynamic and sympathetic response to the "stress" of endotracheal intubation in young and elderly patients and evaluate the mechanism for any changes found.

Methods. Twenty-seven patients, (18-80 yrs; ASA Class I) received diazepam 10 mg PO and atropine 0.4 mg IM 60 min prior to anesthesia for inpatient elective surgery. Following awake baseline recordings of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR), anesthesia was induced with thiopental, 4.0 mg/kg, and succinylcholine, 100 mg. SBP, DBP and HR were recorded at induction after thiopental but before succinylcholine (O time), and 1, 2, 3, 4 and 5 min post-induction. Laryngoscopy and endotracheal intubation was performed 60 sec after induction. Venous blood samples were drawn with the patient awake and 2, 3 and 4 mins post-induction for measurement of plasma norepinephrine concentrations (NE) by a radioenzymatic assay. Samples were also taken with the patient awake for the measurement of β-receptors on lymphocytes using a radioligand binding technique to determine receptor density and receptor affinity for agonists. Informed consent and institutional approval were obtained. Statistical analysis was by non-paired t-test or linear regression as appropriate, $p<0.05$ being taken as significant.

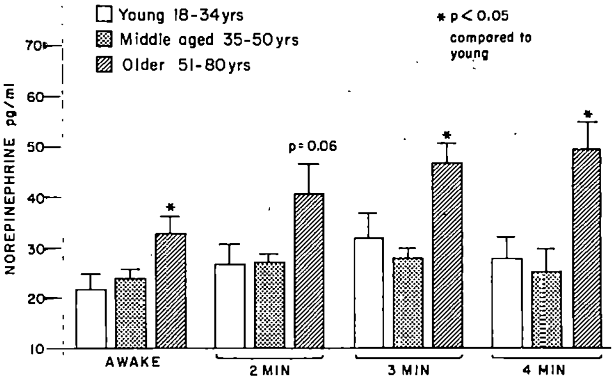
Results. The elderly had a lower heart rate response at 2, 3, 4 and 5 mins post induction so that the maximum increase in heart rate post induction from awake values was negatively correlated with age ($r=-0.66 p<0.001$), Fig 1.

Fig 1: AGE AND MAXIMUM CHANGE IN HR



Baseline SBP and mean BP increased significantly with age ($r=0.81$, $p<0.001$ and $r=0.76$, $p<0.001$ respectively). Age however was not significantly related to the increase in SBP or mean BP that occurred following intubation. NE levels at baseline in awake patients increased with age ($r=0.51$, $p<0.01$). Following intubation, mean plasma NE concentrations were significantly higher in elderly patients than young patients, despite the diminished heart rate response (Fig. 2).

Fig 2: THE EFFECT OF AGE ON NE LEVELS



Thus, in spite of a higher catecholamine response to intubation, the elderly had a lower increase in heart rate. HR per pg/ml of NE was therefore significantly less 2, 3 and 4 mins post induction in elderly patients when compared to young patients (Table).

TABLE: HR per pg/ml NE

		Young 18-34 yr.	Middle Aged 35-50 yr.	Older 51-80 yr.
HR/NE	2 min.	0.54±0.10	0.44±0.03	0.29±0.04*
HR/NE	3 min.	0.46±0.12	0.39±0.04	0.23±0.03*
HR/NE	4 min.	0.51±0.09	0.53±0.13	0.22±0.03*

*p<.05 Mean ± SEM

To determine if this alteration in cardiac sensitivity to catecholamines was reflected by changes in beta receptor function on lymphocytes, beta receptor density and the proportion of receptor binding agonist with high affinity (%RH) - an important determinant of β-receptor sensitivity - were measured. No significant correlation between β-receptor affinity for agonist, %RH, or receptor density was found with age, HR, ΔHR, or HR/NE.

Discussion. Our results indicate that the elderly have a significantly lower chronotropic response to intubation than do the young. As plasma catecholamines were higher in the elderly while the blood pressure rise was not different, this loss of response is not due to either diminished sympathetic responses or altered baroreceptor function. The lack of correlation between direct measures of beta receptor function and the heart rate response to norepinephrine appears to imply a post receptor defect as the mechanism for these changes.

Title: EPINEPHRINE REDUCES NEONATAL GASTRIC FLUID CONTENT OF BUPIVACAINE DURING VAGINAL DELIVERY

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Introduction. The role of epinephrine in reducing placental transfer of local anesthetics is controversial, as evaluated by their fetal/maternal ratios (1,2). Umbilical vein/maternal vein plasma concentration ratios do not indicate the total amount of drug transferred to the fetus, are of limited value in the study of placental transfer and may account for this controversy. Total amount of bupivacaine in gastric fluid of neonates at birth, a proposed new index of placental transfer(3),could reflect the extent of fetal tissue accumulation of the drug. Here it is used in the study of the influence of epinephrine on the placental transfer of bupivacaine following lumbar epidural administration.

Methods. The Clinical Research Committee approved the protocol. Twenty term parturients undergoing epidural anesthesia for labor and delivery and their neonates were studied, under consent. Epidural puncture was performed in the usual manner. Ten patients received 75 mg of 0.5% bupivacaine with epinephrine 1:200.000, and ten patients received the same amount of anesthetic without epinephrine. A section of umbilical cord was doubly clamped prior to placental separation, and heparinized umbilical venous blood samples were collected. Maternal venous blood samples were also collected at the same time. Gastric fluid was suctioned via an orogastric catheter during the first five minutes of life, in an attempt to empty the stomach, the total volume collected being recorded. Maternal and neonatal blood samples and neonatal gastric fluid samples were assayed for bupivacaine concentrations by a gas-liquid chromatographic technique (linearity 0.02 to 5.00 µg/ml, sensitivity 0.02 µg/ml, coefficient of variation within day 0.9%). Neonates were evaluated by Apgar scores at 1 and 5 min. Data were analysed for statistical significance using Students̃ t-test. A P value of less than 0.05 was considered statistically significant.

Results. The patient groups were similar in age, weigth and heigth. Induction to delivery time was also similar in both groups (Table I).All neonates had Apgar scores of 7 or more at 5 min. and there was no significant difference between the incidence of low 1-min. Apgar scores in both groups (Table I). Plasma and gastric fluid levels of bupivacaine are presented in Table II. The fetal-to-maternal ratios of plasma concentrations of bupivacaine were similar. Total amount of bupivacaine in gastric fluid was significantly reduced when using bupivacaine with epinephrine (P ≤0.05).

Discussion. The addition of epinephrine 1:200.000 to bupivacaine solutions does not reduce the UV/MV ratio,although it reduces the amount of drug reaching the gastric fluid. The proposed new index could be advantageous in the study of quantitative distribution of bupivacaine in humans, when compared to other methods used so far (4). It is possible that the gastric fluid content of bupivacaine could reflect the actual accumulation of anesthetic in other vital organs of the neonate.

References
1.THOMAS J,CLIMIE CR,LONG G and NIGHJOY LE . The influence of adrenaline on the maternal plasma levels and placental transfer of lignocaine following lumbar epidural administration.Br J Anaesth 1969; 41: 1029-34.
2. ABBOUD TK,DAVID S,NA GAPPALA S et al. Maternal,fetal and neonatal effects of lidocaine with and without epinephrine for epidural anesthesia in obstetrics. Anesth Analg 1984;63: 973-9.
3. CARVALHO JCA,MATHIAS RS,SENRA WG,SANTOS SRCJ,AMARAL RVG. Bupivacaina no suco gastrico de recem-nascidos apos anestesia peridural para cesariana. XVIII Cong.LatinoAmer. de Anestesiologia,1985, Montevideo.
4. KUHNERT PM,KUHNERT BR,STITTS JM, GROSS TL. The use of a selected ion monitoring technique to study the disposition of bupivacaine in mother,fetus and neonate following epidural anesthesia for cesarean section. Anesthesiology 1981; 55: 611-7.

Table I - Patient and Clinical Data

	Bupivacaine with epinephrine (N = 10)	Bupivacaine plain (N = 10)
Maternal age (yr)	27.60 ± 5.38	23.10 ± 11.26
Maternal weigth (kg)	68.30 ± 7.45	65.55 ± 7.37
Maternal heigth (m)	1.64 ± 0.03	1.61 ± 0.07
ID time (min)	50.40 ± 22.01	74.10 ± 37.77
Apgar scores		
≥7 1 min.	90%	80%
≥7 5 min.	100%	100%

Values are mean ± SD. No significant differences.

Table II - Bupivacaine in plasma and gastric fluid

	Bupivacaine with epinephrine (N = 10)	Bupivacaine plain (N = 10)
Maternal vein (ηg/ml)	463 ± 149	514 ± 236
Umbilical vein (ηg/ml)	164 ± 160	178 ± 102
UV/MV ratio	0.33 ± 0.20	0.38 ± 0.18
Gastric fluid		
concentration (ηg/ml)	316 ± 243	482 ± 256
Vol.of gastric fluid (ml)	9.20 ± 5.58	9.65 ± 6.86
Total amount of bupivacaine (ηg)	*2156 ± 1513	4111 ± 2218

Values are mean ± SD * P≤0.05

Title: EFFECT OF VERAPAMIL ON LIDOCAINE PHARMACOKINETICS AND DYNAMICS IN CONSCIOUS DOGS

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Introduction. Lidocaine (L) is frequently used for regional anesthesia and intraoperative treatment of ventricular cardiac arrhythmias. Because of the increasing number of patients receiving verapamil (V) therapy, there is interest in assessing the pharmacologic interactions between V and L. Rosenblatt et al. reported that V increases the toxicity of L.[1] Howie et al. demonstrated that nifedipine enhanced the cardiovascular toxicity of bupivacaine.[2] Although verapamil causes more cardiac depression than nifedipine, the hemodynamic consequences of lidocaine administration in the presence of verapamil are unknown. Pharmacokinetic interactions might also be expected since both L and V are highly bound to plasma proteins, are high clearance drugs, and V has been reported to decrease hepatic blood flow.[3] This study was designed to assess the effect of V on L hemodynamics and pharmacokinetics.

Methods. Nine 19±3 kg dogs were chronically instrumented for measurement of mean aortic pressure (MAP), left ventricular (LV) dP/dt, cardiac output (CO), and coronary (Cor), carotid (Car) and renal (Ren) blood flows (BF). In the conscious state, each dog received L (1 mg/kg/min, IV for 3 min) alone and in the presence of steady-state V infusion (3 ug/kg/min) on 2 different occasions, randomly assigned and separated by at least 2 days. Hemodynamic function was continuously recorded before and after injecting L. In addition, aortic blood samples for V and L determinations were collected 20 min, 10 min and immediately before L and immediately after and 5, 10, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 5, and 6 hours after L. Concentrations of L and V were analyzed by gas-liquid chromatography using nitrogen-phosphorous detection. L plasma concentrations were fitted to equations formed by a linear sum of 2 exponential terms.[4] Data were analyzed using ANOVA and when significant, paired t-tests were applied. Alpha was set up at the level of 0.05. Data are presented as mean ± SEM.

Results.

Pharmacokinetic: As indicated in Table I, V did not affect the pharmacokinetics of L.

Hemodynamic: L alone induced only a 15% increase in heart rate (HR) from 84±3 bts/min and a 19% decrease in LVdP/dt from 3198±199 mmHg/sec.

When injected in the presence of steady-state V, L elicited an increase of 28% in CO from 2.5±0.2 L/min, 40% in HR from 84±3 bts/min, and a decrease of 28% in LVdP/dt and 29% in systemic vascular resistance (SVR = MAP/CO). Steady-state infusion of V by itself induced a decrease of 15% in SVR from 48±5 units and 10% in LVdP/dt, and an increase of 12% in CO and 19% in HR (Table II).

Discussion. Our data were obtained for lidocaine plasma concentrations within the therapeutic range (6.9 to 5.7 ug/ml) and for verapamil plasma concentration within ranges of those expected to be found in patients preoperatively treated with verapamil and undergoing surgery (60 ng/ml). They indicate that there are minimal hemodynamic and pharmacokinetic interactions between verapamil and lidocaine and that the hemodynamic interactions are mainly additive. It has previously been suggested that caution should be exercised in giving bupivacaine to patients treated with verapamil because verapamil potentiates the cardiac toxicity of bupivacaine.[5] Our data suggest that lidocaine may be more suitable than bupivacaine when local anesthetics are required in patients receiving verapamil preoperatively.

References.

1. Rosenblatt, RM, et al. Anesth. Analg., 1984;63: 26[illegible].
2. Howie, MB, et al. Anesthesiology 1985;63:A225.
3. Ha[illegible]nn, SR, et al. J. Pharmacol. Exp. Ther. 1984; 23[illegible]:301.
4. Holford, NHG. Drug Model, in Public Proceeding Notebook. Bolt, Beranek, and Newman, 1982.
5. Edouard, A, et al. Anesthesiology 1985;63:A257.

TABLE I: Pharmacokinetics of L alone and in the presence of V

		L	L + V
V_1	L	5.3 ± 1.0	5.6 ± 0.9
Intercompartmental Clearance	L/hr	41 ± 10	37 ± 13
Vdss	L	14.3 ± 0.5	15.7 ± 4.5
Total Clearance	L/hr	11.9 ± 0.1	12.9 ± 1.8
B-$t_{1/}$	hr	0.96 ± 0.04	1.38 ± 0.33

TABLE II: Hemodynamic changes from control values following L, V and L + V

		n	L	V	L + V
MAP	mmHg	9	1 ± 4	-4 ± 2	-7 ± 1
CO	L/min	7	0.2 ± 0.1	0.3 ± 0.1*	0.7 ± 0.2†
HR	bts/min	9	13 ± 3*	16 ± 3*	34 ± 3†
LVdP/dt	mmHg/s	8	-610± 50*	-322 ±133*	-901 ± 181†
CorBF	ml/min	7	1 ± 1	6 ± 3	8 ± 4
CarBF	ml/min	6	-2 ± 2	5 ± 13	5 ± 11
RenBF	ml/min	7	-3 ± 3	9 ± 6	9 ± 6
SVR	units	7	-2 ± 3	-7 ± 1*	-14 ± 2†

*p<0.[illegible] vs control; †p<0.05 vs verapamil

Title: SENSITIVITY-ADJUSTED PRIMING CONSISTENTLY ACCELERATES ONSET OF VECURONIUM-INDUCED NEUROMUSCULAR BLOCK IN CATS

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Introduction. Neuromuscular sensitivity varies widely among normal subjects (1). Even an optimal priming dose which will properly prime the majority of subjects may underprime the resistant and overprime the sensitive ones. The present study tested the hypothesis that sensitivity-adjusted priming will accelerate onset of neuromuscular block with improved efficiency and consistency.

Methods. Six healthy adult cats underwent two non-invasive experiments each, Part I and Part II, 6-22 days apart. Anesthesia was induced with halothane 1-2% in air and pentobarbital 10 mg/kg i.v. slowly and maintained on 0.2-0.5% halothane and N_2O 50% in oxygen. Ventilation was controlled for normocarbia. ECG was monitored and esophageal temperature was maintained at 35-37°C. I.V. fluid was maintained at 30-40 ml/kg 0.9% NaCl during the 6-8 hour experiment. The peroneal nerve was stimulated at 0.1 Hz with supramaximal 0.2 ms. rectangular electric pulses from a Grass S88 stimulator. Neurally evoked compound EMG of the tibialis anterior muscle was recorded. At the end of the experiment, the cat was allowed to recover to full consciousness.

Part I experiment was sensitivity-adjusted. Each cat received increnental injections of vecuronium cumulatively for a dose-response curve. The ED_{95} was determined. One hour after complete recovery of twitch and train-of-four, 1/5 of twice the ED_{95} was given as priming dose, followed in 4 min. by 4/5 of twice the ED_{95}. Onset and time course of neuromuscular block was observed. One hour after complete recovery of twitch and train-of-four again, $2ED_{95}$ dose of vecuronium was given as a single bolus. Effects of priming vs. non-priming on onset and time course of neuromuscular block were evaluated by paired t-tests, each cat serving as its own control. Part II experiment was not sensitivity-adjusted, but average-dosed. Instead of individual ED_{95}, the mean ED_{95} of the cats was applied to every cat. The experiment was otherwise the same as Part I. Effects of the average-dosed priming vs. non-priming were likewise determined. In addition, sensitivity-adjusted regimen vs. average-dosed regimen was compared between the two parts for differences in scattering of onset and recovery values, and consistency and magnitude of effect of priming. Paired t-tests and Fisher test for consistency were applied, each cat serving as its own control where appropriate.

Results. Table 1 lists the onset data under all 4 experimental conditions. Table 2 compares the consistency of onset values among the 4 experimental conditions. Statistically significant findings are summed up as follows: (1) Sensitivity-adjusted priming gave the greatest acceleration of onset. (2) Sensitivity-adjusted priming was most consistent in effect. Exceptions did not occur. (3) Average-dosed priming was effective, but less so. Exceptions did occur. While sensitivity-adjusted regimen improves the magnitude and consistency of acceleration of onset, it did not alter the subsequent time course of recovery.

Discussion. Our results indicate that given the average mg/kg dose of vecuronium, cats vary markedly in neuromuscular responses in all onset and recovery parameters. Individualization of the paralyzing dose alone by adjusting the dose to sensitivity reduces the scattering of results. Individualization of the priming dose likewise improves the consistency and average magnitude of priming effect. Several aspects of priming are matters of controversy in clinical anesthesia (2). It is implied that sensitivity-adjusted priming may also improve the results and reduce chances of overpriming and underpriming clinically under similar conditions.

References.

1. Katz RL. Neuromuscular effects of d-tubocurarine, edrophonium and neostigmine in man. Anesthesiology 1967; 28:327.
2. Miller RD. The priming principle. Anesthesiology 1985; 62:381.

Table 1. Onset of vecuronium-induced neuromuscular block (in seconds) from injection of paralyzing dose to occurrence of neuromuscular block >95%

	sensitivity-adjusted regimen		average-dosed regimen		acceleration ratios	
Cat #	priming (I')	non-priming(I)	priming(II')	non-priming(II)	(I')/(I)	(II')/(II)
1	60	100	70	110	.60	.64
2	110	160	120	180	.69	.67
3	110	140	150	170	.79	.88
4	50	90	80	90	.56	.89
5	110	180	260	250	.61	1.04
6	110	150	50	60	.73	.83
mean	92	137	122	143	.67	.83
S.D.	29	35	77	70	0.1	0.15
S.E.M.	12	14	31	29	0.04	0.06

paired t tests

$p<0.001$ $p<0.1$ $p<0.1$

$p>0.5$

$0.2>p>0.1$

$p>0.5$

$p = 0.1$

Table 2. Consistency of speed of onset, vecuronium-induced neuromuscular block in cats. (For original data, see Table 3.)

	Sensitivity-adjusted regimen		Average-dosed regimen	
	priming(I')	non-priming(I)	priming(II')	non-priming(II)
S.D./mean	0.32	0.26	0.63	0.49
min-max	60-110	90-180	70-260	60-250
range	50	90	190	190
range/mean	0.54	0.66	1.56	1.33
variance	4084	6134	29484	24334

F test*

$p>0.25$ $p>0.25$

$0.025<p<0.1$

$0.025<p<0.1$

$0.005<p<0.025$

$0.025<p<0.1$

Title: THE EFFECT OF NITROUS OXIDE-FENTANYL ANESTHESIA ON VISUAL EVOKED POTENTIALS IN HUMANS

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Introduction. Visual evoked potentials (VEP) are used in monitoring the functions of the visual pathways during certain neurosurgical procedures. Preferably, the anesthetic agents which affect the VEP minimally should be utilized in order to interpret them effectively. Only a few studies are available dealing with the effects of anesthetic agents on the VEP.[1,2] We decided to study the effects of nitrous oxide-fentanyl anesthesia on the VEP in unpremedicated patients.

Methods. This study was approved by our Institutional Review Board. Nine consenting healthy female patients (age 20-38 years) undergoing gynecological procedures were studied. No premedication was given to the subjects. The evoked potentials were recorded from the occipital electrode (O_z) in reference to the vertical electrode (C_z) using one of the mastoid electrodes as a ground. Recordings were made on a Nicolet Pathfinder I. Impedance was maintained at less than 3000 ohm. The bandpass filter was set at 1-200 Hz and the sensitivity was set at 100 µV full scale. Monocular flash stimuli was presented over the patient's closed left eye at a rate of 1.9 Hz with a duration of 10 msec. Each averaging epoch was set at 500 msec with a total of 100 repetitions.

Control VEP were recorded before induction of anesthesia in unpremedicated patients. Then, anesthesia was induced with 0.05 mg/kg of d-tubocurarine, 4 µg/kg of fentanyl, and 3-4 mg/kg of thiopental followed by 1.5 mg/kg of succinylchlorine I.V. Patients were intubated and ventilation was controlled to maintain end-tidal P_{CO_2} within 35-40 mmHg. Anesthesia was maintained with vecuronium, 60% nitrous oxide-40% oxygen, and a bolus of 50-100 µg of fentanyl every 20-30 min as needed according to changes in blood pressure and pulse rate. Body temperature was sustained between 35-36°C, while systolic blood pressure was maintained with fentanyl and an intravenous infusion of Ringer's lactated solution within ± 25% of the preoperative level. Thirty minutes after induction, the second VEP was recorded. The latencies of N1 and P1 (P100) were measured. Amplitude was measured as the vertical distance between N1 and P1.

For data analysis, paired Student's t test was used. A p value below 0.05 was considered statistically significant.

Results. The VEP were obtained in a reproducible manner in all the patients studied. The total dose of fentanyl given during the 30 min period from the induction of anesthesia to the recording of the VEP ranged from 5-6 µg/kg. No patient had recall or awareness of intraoperative events. The latencies of both N1 and P1 were significantly increased over the control (average +17.4% and 15.6% each). There was no significant change in amplitude. (Table 1). A typical wave form is shown in Figure 1.

Discussion. Our study suggests that the interpretation of the VEP would be easier when nitrous oxide-fentanyl anesthesia is used since there is only a slight increase in the latency with no significant change in the amplitude. To the contrary, isoflurane significantly changes both the latency and amplitude.[2]

References.

1. Uhl RR, Squires KC, Bruce DL, Starr A. Effects of halothane anesthesia on the human cortical visual evoked response. Anesthesiology 1980; 53:273-276.
2. Chi OZ, Field C. Effects of isoflurane on visual evoked potentials in humans. Anesthesiology 1986; 65:328-330.

Table 1

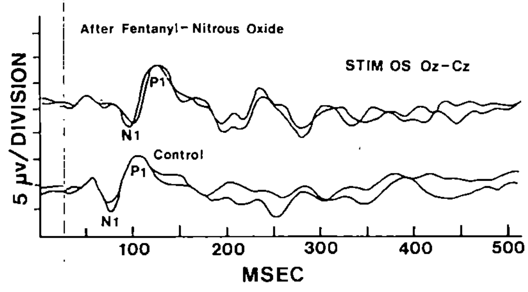
VISUAL EVOKED POTENTIAL LATENCIES AND AMPLITUDES

	Latency (msec±SD)		Amplitude (µV±SD)
	N1	P1	
Control (n=9)	83.4±10.5	105.8±9.2	8.06±3.55
Nitrous Oxide—Fentanyl (n=9)	97.9±9.5	122.3±7.3	7.08±3.10
	(+17.4%)	(15.6%)	
Significance	p<0.0025	p<0.0005	NS*

*No statistical significance

Figure 1

TYPICAL VEP WAVE FORM OBTAINED FROM ONE PATIENT THIRTY MINUTES FROM INDUCTION



Title: INTRAOCULAR PRESSURE AFTER "CRASH" INDUCTION WITH VECURONIUM OR ATRACURIUM PLUS LOW-DOSE NARCOTICS

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Introduction. Anesthetic induction for the open-eye injury patient with a full stomach requires protection against both aspiration and sudden increases in intraocular pressure (IOP). Intubating doses of the nondepolarizing relaxants atracurium and vecuronium have no adverse effects on IOP, but laryngoscopy and intubation do result in dramatic increases in IOP (1). We undertook this study to determine whether low-dose sufentanil or fentanyl might attenuate or eliminate adverse IOP responses to intubation during rapid sequence induction with vecuronium or atracurium.

Methods. This study was approved by the institution's Human Investigation Committee, and written informed consent was obtained from each patient. Forty adult surgical patients, ages 19-68 and ASA class I or II, were randomly assigned into 4 groups of 10 each. Baseline IOP measurements were obtained for each patient by pneumotonometry after application of topical anesthesia. In each patient, following 3 minutes of preoxygenation, rapid sequence induction was performed using thiopental 5 mg/kg followed immediately by a narcotic (either sufentanil 1 µg/kg or fentanyl 5 µg/kg) and a muscle relaxant (either vecuronium 0.2 mg/kg or atracurium 1 mg/kg). Cricoid pressure was applied, and IOP was measured 1 min later. Intubation was then performed, and controlled ventilation with 67% N_2O in O_2 was begun, with end-tidal CO_2 maintained between 35-40 mmHg for the remainder of the study period. Intraocular pressure measurements were performed and recorded immediately after intubation and every min for the next 5 min. Patients in Group 1 received the combination of sufentanil 1 µg/kg and vecuronium 0.2 mg/kg, and those in Group 2 received sufentanil 1 µg/kg and atracurium 1 mg/kg. Patients in Group 3 received fentanyl 5 µg/kg and vecuronium 0.2 mg/kg, while those in Group 4 received fentanyl 5 µg/kg and atracurium 1 mg/kg. Data were analyzed using paired t-tests and one-way analysis of variance. $P<0.05$ was regarded as significant.

Results. In all 4 groups, IOP decreased significantly 1 min after induction as compared to awake (baseline) IOP (Table). In no group did post-intubation IOP reach or exceed the awake value. In fact, in Groups 1 and 2, all IOP values after those immediately post-intubation were significantly less than the awake values. The highest post-intubation IOP occurred immediately after intubation in all four groups. No patient developed chest wall rigidity. Intubating conditions were very good to excellent (laryngoscopy performed easily with no patient movement prior to intubation, vocal cords relaxed) in all patients 60 sec after induction. Six of the 40 patients (2 in Group 1 and 4 in Group 4) coughed slightly after intubation without marked changes in IOP. Four patients (1 in Group 1, 1 in Group 2, and 2 in Group 4) required ephedrine for decreased blood pressure, and all responded promptly. Three patients (2 in Group 2 and 1 in Group 3) required naloxone to antagonize narcotics and allow safe extubation at the end of their surgical procedures. Twelve of the 20 patients receiving atracurium (4 in Group 2 and 8 in Group 4) developed a "flush" reaction, presumably due to histamine release. No intra- or post-operative respiratory problems occurred.

Discussion. Recent studies (1,2) have shown the effectiveness of large doses of intermediate-duration nondepolarizers for rapid sequence induction. The results of our study support the conclusion that satisfactory intubating conditions are present 60 sec following the administration of either vecuronium 0.2 mg/kg or atracurium 1 mg/kg, with no adverse effects on IOP. Increases in IOP secondary to laryngoscopy and intubation (1) were prevented by the administration of low-dose narcotics, either sufentanil 1 µg/kg or fentanyl 5 µg/kg following thiopental at the beginning of the rapid induction sequence. Similar doses of these narcotics have been demonstrated to blunt the cardiovascular responses to laryngoscopy and intubation (3,4), and thus it is not unexpected that relative IOP stability accompanied their use. The adverse effects of the induction method we employed do not appear to contraindicate this technique when protection from elevated IOP is a consideration in anesthetic management.

Table. Intraocular Pressure (mmHg)

	Awake	1 Min After Induction	Immediately After Intubation	Time After Intubation (Min)				
				1	2	3	4	5
Sufentanil 1 mg/kg + Vecuronium 0.2 mg/kg (Group 1)	19±2	14±2*	16±1	14±1*	13±1*	12±2*	13±1*	13±1*
Sufentanil 1 mg/kg + Atracurium 1 mg/kg (Group 2)	22±1	16±1*	20±1	17±1*	16±1*	16±1*	16±2*	16±1*
Fentanyl 5 µg/kg + Vecuronium 0.2 mg/kg (Group 3)	18±1	14±1*	16±1	16±2	16±2	16±2	15±1	13±1*
Fentanyl 5 µg/kg + Atracurium 1 mg/kg (Group 4)	17±1	12±1*	17±1	16±1	14±1*	14±1*	13±1*	14±1*

All values are mean ± SE
*Significantly different from awake value ($p<0.05$)

References.

1. Schneider MJ, Stirt JA, and Finholt DA. Atracurium, vecuronium and intraocular pressure in man. Anesth Analg 1986; 65:877.
2. Lennon RL, Olson RA, and Gronert GA. Atracurium or vecuronium for rapid sequence endotracheal intubation. Anesthesiology 1986; 64:510.
3. Kleinman J, Marlar K, Silva DA, Miller R, and Kaplan JA. Sufentanil attenuation of the stress response during rapid sequence induction. Anesthesiology 1985; 63:A379.
4. Martin DE, Rosenberg H, Aukburg SJ, et al. Low-dose fentanyl blunts circulatory responses to tracheal intubation. Anesth Analg 1982; 61:680.

Title: MORPHINE INHALATION VERSUS INTRAVENOUS INFUSION IN PAIN TREATMENT AFTER ABDOMINAL SURGERY

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Introduction. The aim of the present study was to investigate morphine via inhalation and intravenous infusion in pain treatment after abdominal surgery.

Methods. With institutional approval, 20 patients (6 male, 14 female, ASA I-II) scheduled for abdominal surgery in nitrous-oxide/halothan/relaxant anaesthesia were included in the study after giving their informed consent. Postoperatively, all patients received oxygen via mask and, when complaining of worst pain, were randomly given for constant analgesia either a continuous-plus-on-demand infusion of morphine (1) into the nebulization reservoir in the oxygen supply (Group I) or intravenously (Group II); initial bolus 1.5 mg; basal infusion 1.5 mg; bolus on-demand 0.6 mg. At varying intervals (0,30 ,1h,2h,3h,4h,6h,9h, 12h) blood pressure, heart and respiratory rate were recorded and blood samples were taken to determine arterial blood gases and, in 14 patients free morphine immunoreactivity (FMI) by radioimmunoassay (Diagnostic Products Corporation, Los Angeles, cross reactivity to morphine-3-glucuronide 0.22%). For statistical analysis the t-test for unpaired data was employed.

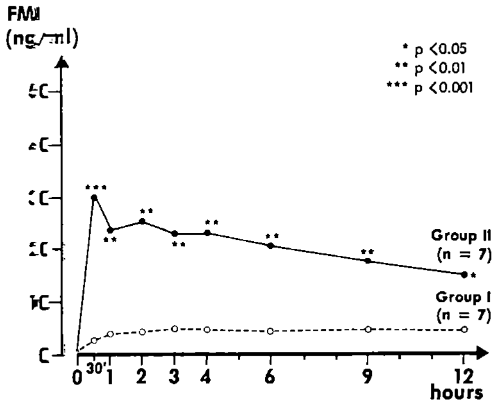
Results (mean ± sem). Analgesia was attained within 34 ± 9 (Group I) and 16 ± 3 (Group II) minutes. For constant analgesia patients of Group I required a total of 21.2 ± 0.4 mg (range: 19.5 - 23.1 mg), of Group II 22.6 ± 0.8 mg (20.1 - 28.5 mg) (n.s.). There was no significant difference in blood pressure, heart and respiratory rate obtained between the two groups. pCO2 remained normal in all patients. The incidence of side-effects is shown in Table 1. FMI of Groups I and II reached plateaus of around 4 ng/ml and 20 ng/ml, respectively (see Fig.1).

Discussion. From the above results it was concluded that nebulized morphine is as effective in treatment of pain after abdominal surgery as intravenous morphine and that the lower incidence of side-effects and the easy application make morphine inhalation preferable to morphine intravenous infusion. The pharmacokinetic behavior of serum morphine demonstrates that in comparison with the 100% bioavailable intravenous morphine, only part of the inhaled morphine reaches the systemic circulation via mucuous membranes and lung. This suggests that a potent analgesic derivative might be transformed during the passage of absorption (2).

TABLE 1
SIDE-EFFECTS UNDER THE TREATMENT

Group	I	II
sedation	6 (10)	10 (10)
micturition	-	3 (10)
nausea + emesis	-	2 (10)

FIG. 1



Group I : Continous + on-demand inhalation of morphine

Group II : Continous + on-demand intravenous infusion of morphine

References
1) Chrubasik J, Wiemers K: Continuous-plus-on-demand epidural infusion of morphine for postoperative pain relief by means of a small, externally worn infusion device. ANESTHESIOLOGY 1985; 62:263-7.
2) Chapter: Chrubasik J, Falke, Zindler M, Geller E, Niv D, Friedrich G, Schulte-Mönting J: Indication for pulmonary metabolism of morphine?, Schmerz/Pain/Douleur 7. Edited by W.F. Ahnefeld.Heidelberg/FRG, Fischer Press, 1986, pp 36-38

Title: REDUCED CONFUSION - SPINAL OR GENERAL ANAESTHESIA IN THE ELDERLY

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Introduction. As the population ages and surgical and anaesthesiological techniques advance, more surgery is undertaken on older patients. Psychological problems, particularly preoperative anxiety and postoperative confusion contribute to morbidity and mortality, and the contribution of anaesthesia is difficult to ascertain, and review of the recovery of mental function postoperatively is inconclusive (1,2). Tests of mental function were not performed on the day of operation, or first postoperative day to compare mental recovery after general anaesthesia (GA) or spinal anaesthesia (SA) in elderly patients. The purpose of this study was to compare mental recovery in elderly patients from GA or SA and to examine the hypothesis that spinal anaesthesia (SA) was associated with less post-operative confusion than general anaesthesia (GA).

Methods. The protocol was approved by the Human Ethics Committee, and informed consent was obtained. Forty-four patients, aged 60 and over, scheduled for transurethral resection of prostate or pelvic floor repair were randomised either to GA or SA. No premedication was given. GA was induced with sleeping dose of pentothal 2-5 mg/kg and fentanyl 1-2 ug/kg. Pre-curarization by 3 mg d-tubocurarine was followed by muscle relaxation with 1.5 mg/kg suxamethonium. The trachea was intubated. Anaesthesia was maintained with nitrous oxide, oxygen, curare, fentanyl, and isoflurane. SA was done at L3-4, L4-5 interspace with 22 or 26 gauge spinal needle. Tetracaine, 10-14 mg diluted in 10% dextrose solution, was given. Psychological assessment included pre-operative cognitive screening by Mini Mental State test, measurement of anxiety by visual analogue scale, and standarized geriatric mental status examination. Mini Mental Status examination was administered pre-op, six hours after surgery, and on 1, 3, 5, days, and one month post-op. Anxiety was measured pre-op and 1 day post-op. Assessment included also history, medication, anaesthetic data, and laboratory investigation pre-op and post-op.

Results. The mini mental state (cognitive function) showed that patients with SA scored better at all times compared with the GA group. Mean change in mental function score was statistically significant in the GA group as compared to the SA group at six hours ($p<0.001$) and third day ($p<0.1$) (fig. 1) post-op. More antiemetic was required by GA than SA ($p<0.005$). There were no significant differences in pre and post-op. anxiety levels, blood work, or post-op. analgesic and hypnotic use. Of 44 competent fit patients, 3 demonstrated postoperative confusion all in GA group (12.5%). None of the patients in the SA group showed signs of confusion. Two of the 3 confused patients were on antidepressant hypnotic pre-op.

Discussion. Mental recovery post-op. was better with SA as compared to GA, and significant mental impairment occurred at six hours and three days after GA. A higher percentage of patients who received GA were confused as compared to SA. Comparison of pre-op personality characteristics, anxiety levels, and medication - particularly antidepressants, taken by 2 of the 3 confused patients indicate approaches to pre-op prediction of vulnerability and choice of anaesthetic.

References.
1. Hole, A., Terjesen, T., Brievik, H. Epidural Vs general anaesthesia for total hip arthroplasty in elderly patients. Acta anaesth scand 24: 279-287 1980.
2. Riis, J., Lomholt, O. Immediate & longterm recovery from general versus epidural anaesthesia in elderly patients. Acta anaesth scand 27: 44-49, 1983.

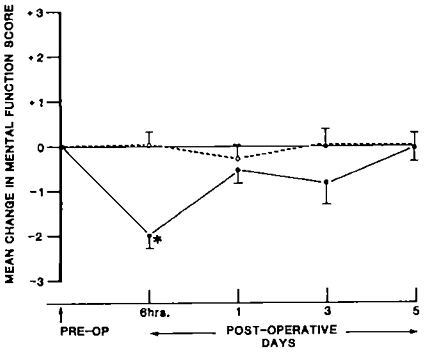

Fig. 1.
Mean change in mental function score in patients having general anaesthesia (---) versus spinal anaesthesia (....) * $p<.001$

Title: BEAGLE PUPPY MODEL OF THE NEONATAL BRAIN: EFFECT OF HALOTHANE ON REGIONAL BLOOD FLOW AND METABOLISM

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Introduction The effects of anesthetics on the cerebral circulation in newborn infants is extrapolated from data derived from adult human and animal studies.[1] Information on neonatal cerebral blood flow autoregulation and cerebral metabolism has been obtained from experiments done in beagle puppies.[2] We have used this model to determine the effects of halothane on regional cerebral blood flow (rCBF).

Methods Pure-bred beagle pups 2 to 6 days of age and 350 to 700 grams were studied. Anesthesia was induced with halothane, nitrous oxide and oxygen by mask. Tracheostomy was performed followed by neuromuscular paralysis with intraperitoneal vecuronium. Ventilation was controlled using a Harvard Rat Ventilator, to maintain $PaCO_2$ at 35-40 mmHg. Anesthesia was continued with 70% nitrous oxide and 30% oxygen. One femoral venous and two arterial lines were placed for fluid administration, blood pressure and blood gas monitoring, and microsphere withdrawal. A catheter was advanced from the carotid artery into the left ventricle for injection of 15 micron microspheres (57 Co, 113 Sn, 46 Sc). A sagittal sinus catheter was placed for measurement of cerebral venous O_2 content. All incisions were made and catheters placed after local infiltration with 0.5% bupivacaine. Blood loss was replaced with adult dog whole blood and mean arterial blood pressure maintained with infusions of methoxamine or epinephrine. Halothane was discontinued for one hour prior to beginning the study. Cerebral blood flow to the grey matter of the frontal cortex (FC) and parietal cortex (PC), cerebellum (Ce), thalamus (Th) and subcortical white matter (Wh) regions were obtained at baseline, and at 0.5% and 1.0% halothane. $CMRO_2$ was also determined at these levels.

Results The results are expressed in Figure 1 as percent of control values, and analyzed by paired t-test. Data is presented for normotensive animals only. Hemodynamically unstable pups were excluded from the study. There was a significant increase in rCBF to all areas except the PC at 1.0% halothane, and a significant decrease in $CMRO_2$. No significant changes were found at 0.5% halothane.

Discussion Halothane in this model shows a dose dependent increase in CBF and a decrease in $CMRO_2$. These results are similar to those found in adult animals[3] and humans[1] and suggest that there are no age related differences in cerebral metabolic activity or hemodynamics in response to halothane. However, the distribution of CBF during hypotension or asphyxia differ in newborn[2] and adult dogs.[4] How inhalational anesthetics effect these responses in the newborn is currently under investigation.

References

1. Smith AL, Wollman H: Cerebral blood flow and metabolism: Effects of anesthetic drugs and techniques. Anesthesiology 36:378-400, 1972
2. Ment LR, Stewart WB, Duncan CC, et al: Beagle puppy model of perinatal cerebral infarction. J Neurosurg 63:441-447, 1985
3. Theye RA, Michenfelder JD: The effect of halothane on canine cerebral metabolism. Anesthesiology 29:1113-1118, 1968
4. Artru AA, Michenfelder JD: Canine cerebral metabolism and blood flow during hypoxemia and normoxic recovery from hypoxemia. J Cereb Blood Flow Metab 3:277-283, 1981

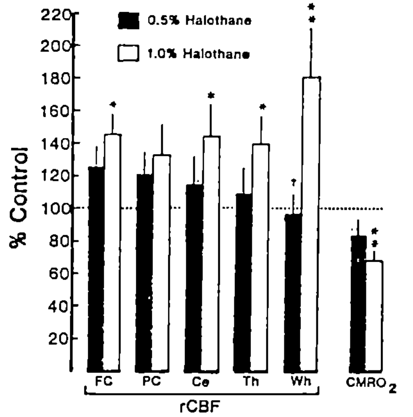

Fig. 1. Effects of halothane on cerebral cortical O_2 utilization ($CMRO_2$) and regional CBF. Expressed as % control ± SEM. * $P<0.05$, ** $P<0.01$ compared to control; † $P<0.05$ compared to 1.0% halothane.

Title: HISTAMINE AND HEMODYNAMIC RESPONSE AFTER ATRACURIUM VS. VECURONIUM

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Introduction. Previous studies have not correlated the cardiovascular changes seen following atracurium administration to changes in serum histamine levels.[1] [2] This study was undertaken to determine the individual cardiovascular responses of cardiac surgical patients to the administration of equipotent, intubating doses of atracurium and vecuronium and to correlate these responses to changes in serum histamine levels.

Methods. Eighteen patients scheduled for elective coronary artery bypass surgery were studied after informed consent. All patients received lorazepam (1-2 mg PO), morphine (0.1 mg/kg IM) and scopolamine (0.3-0.4 mg IM) two hours prior to the induction of anesthesia. Anesthesia was induced with fentanyl (150 µg IV) and lorazepam (4 mg IV). Mask ventilation with 100% inspired oxygen was maintained throughout the period of study. Patients were randomly assigned to two groups in a double blind fashion. Group I patients received Atracurium 0.5 mg/kg, whereas Group II patients received vecuronium 0.12 mg/kg. Two minutes following induction, control hemodynamic measurements and baseline serum histamine levels were obtained. The muscle relaxant was then administered as a bolus. Hemodynamic measurements and serum histamine levels were then repeated at 2, 5, and 10 minutes after drug administration. Hemodynamic measurements included heart rate (HR), systemic blood pressure (SBP), pulmonary artery pressure (PAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO). Systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), and stroke volume were calculated from the above data. Serum histamine levels were determined by radioenzymatic analysis. Analysis of the data was with Student's t-test for paired and group data (Bonferroni correction) and linear regression. Significance was defined as $p < 0.05$.

Results. In Group I (Atracurium), the percent change in serum histamine levels from baseline was significant at each interval of measurement ($p < 0.05$). This was associated with a significant increase in cardiac output and decrease in systemic vascular resistance at each time point ($p < 0.05$). Systolic, diastolic and mean systemic arterial pressure were also significantly decreased 2 min following atracurium administration ($p < 0.05$).

In Group II (Vecuronium), no significant changes were noted regarding serum histamine levels or hemodynamic variables. Table 1 and Figure 1 show that the changes in serum histamine levels correlated significantly to changes in mean arterial pressure at both the two and five min intervals in those patients given atracurium, whereas no such correlations existed in the vecuronium group.

Discussion. Recommended intubating, equipotent doses, which were 2.5 times the ED_{95} for neuromuscular blockade, were utilized. Used within this clinical dose range, vecuronium was found to produce less histamine release and greater hemodynamic stability than atracurium. Additionally, the percent change in mean arterial pressure in response to atracurium correlated well with the percent change in serum histamine levels. Serum histamine levels did not correlate with changes in mean arterial pressure in response to vecuronium.

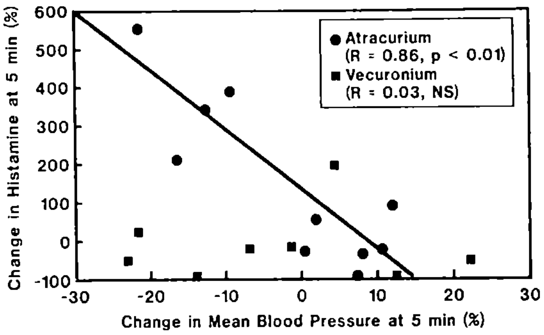
From these findings, we conclude that, when utilizing the above clinical dose range, the cardiovascular changes following the administration of atracurium are due to the release of histamine. Thus, in patients with cardiac disease in whom the cardiovascular sequelae of histamine release are undesirable, the use of vecuronium may be preferred over that of atracurium.

References
1. Morris RB, Cahalan MK, Miller RD, et al: Anesthesiology 58:438, 1983.
2. Miller RD, Rupp SM, Fisher DM, et al: Anesthesiology 61:444, 1984.

Atracurium vs Vecuronium
Correlations of % Change Histamine
with % Change in MAP

		R	p	n
Total Population	2 min.	-0.42	0.04	18
	5 min.	-0.44	0.03	18
	10 min.	-0.07	0.39 (ns)	18
Atracurium	2 min.	-0.57	0.04	10
	5 min.	-0.86	<0.01	10
	10 min.	-0.38	0.14 (ns)	10
Vecuronium	2 min.	-0.01	0.49 (ns)	8
	5 min.	0.03	0.47 (ns)	8
	10 min.	-0.18	0.33 (ns)	8

Histamine and Blood Pressure



Title: LACK OF TRANSMURAL PLASMA SKIMMING IN LEFT VENTRICULAR FREE WALL IN ISOVOLEMIC HEMODILUTION IN DOGS

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Introduction. A peripheral layer of plasma is created in blood vessels by the tendency of red blood cells for axial streaming (1). Under conditions of high flow rate, this cell-free zone of plasma may be directed preferentially into a branch vessel, a phenomenon termed plasma skimming (2). The sharp angles with which intramural coronary vessels branch from transmurally penetrating arteries favors plasma skimming in the superficial layers of the left ventricular free wall. Although previous studies demonstrated transmurally uniform microvascular hematocrit in the left ventricular free wall under control conditions (3), we postulate that this may not be the case during hemodilution when plasma skimming would be favored by increased velocity of red blood cells and expanded peripheral layer of plasma. Accordingly, the present study was conducted in which transmural variation in microvascular hematocrit was evaluated in the left ventricular free wall of the canine heart under control conditions and during acute isovolemic hemodilution (HD). Measurements of regional microvascular blood volume, an index of open capillary density (3), regional myocardial blood flow, and global left ventricular oxygen consumption were also obtained.

Methods. Nine large, mongrel dogs were anesthetized with sodium pentobarbital. After intubation and left thoracotomy, animals were mechanically ventilated with room air supplemented with oxygen. Mean arterial pressure (MAP), mean left atrial pressure (MLAP), and left ventricular pressure (LVP) were measured. LVP was differentiated to give dP/dt max and used to drive a cardiotachometer.

Measurements of regional myocardial microvascular hematocrit (RMHCT) and regional myocardial microvascular blood volume (RMBV) were obtained by indicator-dilution using ^{51}Cr-red blood cells and ^{59}Fe-plasma siderophilin (3). Large vessel hematocrit (LVHCT) was obtained by centrifugation. Radioactive microspheres (15 μ) were injected into the left atrium to measure regional myocardial blood flow (3). A cannula was placed in coronary sinus to obtain samples of venous effluent from left ventricular myocardium. These samples along with samples of arterial blood were analyzed for oxygen content so that left coronary arteriovenous oxygen content difference could be calculated and multiplied by average left ventricular myocardial blood flow to yield myocardial oxygen consumption (MVO$_2$)

HD was produced by removing blood from a carotid artery at a rate of 20 ml/min while replacing it with 6 % dextran (molecular weight 40,000) in saline at the same rate. The total volume exchanged was 45 ml/kg body weight. Values were obtained after preparation was permitted to stabilize for 30 min following completion of fluid exchange. Statistical analyses were performed using standard tests.

Results. Under control conditions, values (mean ± S.E.) for systemic hemodynamic and arterial blood gases were unremarkable (MAP, 102 ± 12 mmHg; MLAP, 1.6 ± 0.6 mmHg; dP/dt max, 2180 ± 270 mmHg/sec; heart rate, 160 ± 5 beats/min; PO$_2$, 120 ± 26 mmHg; PCO$_2$, 36 ± 2 mmHg; pH, 7.38 ± 0.02; LVHCT, 45 ± 3 %). HD had no effect on these parameters with the exception that it reduced MAP and LVHCT to 78 ± 9 mmHg and [illegible] ± 4 %, respectively.

Values for RMHCT and RSBV are presented in Table 1. Under control conditions (C) RMHCT was less than LVHCT and was transmurally uniform; RMBV showed transmural gradient favoring subendocardium. HD lowered RMHCT in all transmural layers, although reduction was less than proportional to fall in RMHCT. Also, HD reduced slightly mean transmural RMBV, but it had no effect on endo>epi gradient.

MVO$_2$ averaged 10.0 ± 2.3 ml/min/100g under control conditions and was not altered by HD; increases in myocardial blood flow (83 ± 12 vs. 189 ± 33 ml/min/100g) were sufficient to offset reductions in coronary arteriovenous oxygen content difference (11.[illegible] ± 1.4 vs. 5.8 ± 1.0 vol %). No significant transmural gradient for regional myocardial blood flow was evident under either control conditions or HD.

Discussion. Uniform microvascular hematocrit across left ventricular free wall during HD indicated no transmural plasma skimming. This finding is consistent with the well-maintained global myocardial oxygenation and function which were demonstrated. Reduced hematocrit in coronary microvessels has been demonstrated previously (3), and likely reflects the Fahraeus effect (1). The relative preservation of microvascular hematocrit observed in heart during HD is new finding which warrants further investigation. The microvascular blood volume data suggest transmural gradient of myocardial open capillary density, favoring subendocardium. This finding is in agreement with previous reports (3), and is in keeping with higher O$_2$ requirement, but similar blood flow, in subendocardium compared to subepicardium (4).

References

1. Fahraeus R. The viscosity of blood in narrow capillary tubes. Am J Physiol 1931; 96:562-568

2. Keele CA, Neil E. Samson Wrights Applied Physiology: London: Oxford University Press, 1971:75.

3. Crystal GJ, Downey HF, Bashour FA. Small vessel and total coronary blood volume during intracoronary adenosine. Am J Physiol 1981; 241 (Heart Circ Physiol 10): H[illegible]94-H201

4. Weiss HR, Neubauer JA, Lipp JA, Sinha AK. Quantitative determination of regional oxygen consumption in the dog heart. Circ Res 1978; 42: 394-4[illegible]

Table 1. Effects of Hemodilution on RMHCT and RMBV

	RMHCT (%)		RMBV (ml/100g)	
	C	HD	C	HD
EPI	37 ± 2	17 ± 3	4.3 ± 0.2	3.7 ± 0.1
MID	37 ± 2	16 ± 4	4.8 ± 0.1	4.2 ± 0.1*
ENDO	35 ± 3	15 ± 4	4.9 ± 0.3*	4.7 ± 0.4*
TRANSMURAL	36 ± 2	16 ± 3	4.6 ± 0.1	4.2 ± 0.1

Values are Mean ± S.E. * P<0.05, different from EPI.

Supported by NIH GRANT HL-33803.

Title: MYOCARDIAL OXYGENATION IN SELECTIVE CORONARY HEMODILUTION IN DOGS: EFFECT OF CORONARY INSUFFICIENCY

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Introduction. Isovolemic hemodilution is increasingly used as a method of blood conservation. In a previous report (1), we described studies in which myocardial effects of selective coronary hemodilution were evaluated. These studies demonstrated well-maintained myocardial oxygen consumption and segment shortening in the face of severe reductions in coronary hematocrit to less than 15%, because increases in coronary blood flow were sufficient to offset induced reductions in oxygen extraction. Analysis of reactive hyperemic responses demonstrated that coronary vasodilation along with reduced blood viscosity contributed to these increases in coronary blood flow (2), which inferred reduced tolerance of myocardium to hemodilution in the presence of exhausted coronary vasodilatory reserve capacity. The present study was designed to test this notion directly by evaluating influence of coronary insufficiency on changes in myocardial oxygen consumption and related parameters during selective coronary hemodilution.

Methods. Seventeen large, mongrel dogs were anesthetized with sodium pentobarbital. After intubation and left thoracotomy, the animals were mechanically ventilated with room air supplemented with oxygen. Mean arterial pressure (MAP), mean left atrial pressure (MLAP), and left ventricular pressure (LVP) were measured. LVP was differentiated to give dP/dt max and used to drive a cardiotachometer.

The left anterior descending coronary artery (LAD) was cannulated and perfused via an extracorporeal system. The perfusion system utilized two reservoirs; one contained normal arterial blood (NB) and the other contained arterial blood diluted with lactated Ringer's solution to hematocrit (HCT) 50% of control. To cause selective coronary hemodilution (HD), the LAD perfusion field was switched from normal blood reservoir to low HCT reservoir. LAD perfusion pressure was maintained with compressed gas at a level near MAP (94 ± 3 mmHg) during NB and HD, and it was also set to 50% of that level during HD to simulate coronary insufficiency (CI). The reduction in perfusion pressure abolished reactive hyperemic response to 90 sec occlusion, indicating exhausted vasodilatory reserve capacity. Coronary blood flow (CBF) via the LAD perfusion line was measured with an electromagnetic flow transducer and meter.

The anterior ascending coronary vein was cannulated at same level as the LAD so that the local arteriovenous oxygen content difference ($C(a-v)O_2$) could be determined and used in Fick equation to compute local myocardial oxygen consumption (MVO_2). Measurements of myocardial segment length in LAD bed were obtained with ultrasonic crystals. Percent segment shortening (%SS) was calculated from the formula, %SS = (End-diastolic length - End-systolic length)/ End-diastolic length. Transmural distribution of CBF was determined with 15 μ radioactive microspheres (3). Measurements were obtained after attainment of steady-state hemodynamic conditions during selective LAD hemodilution, usually 3 min after change in coronary perfusion condition. Statistical analyses were performed using ANOVA and Student-Newman-Keuls test. P<0.05 was considered significant.

Results. Coronary and myocardial effects of selective coronary hemodilution are presented in Table 1. With perfusion pressure at control levels during hemodilution, increased coronary blood flow compensated for reduced oxygen extraction, which maintained oxygen consumption and segment shortening constant. This was not the case when hemodilution was combined with coronary insufficiency. Under this condition, coronary blood flow was no greater than control resulting in reduction in myocardial oxygen consumption and segment shortening. EPI/ENDO ratios indicated transmurally uniform myocardial blood flow under control conditions and during hemodilution alone, but a transmural gradient favoring the subepicardium during hemodilution combined with coronary insufficiency.

Under control conditions, values (mean ± S.E.) for systemic hemodynamic and arterial blood parameters were unremarkable (MAP, 83 ± 4 mmHg; MLAP, 5.3 ± 0.6 mmHg; dP/dt max, 1255 ± 55 mmHg/sec; heart rate, 142 ± 5 beats/min; PO_2, 126 ± 15 mmHg; PCO_2, 37 ± 4 mmHg; pH, 7.36 ± 0.01; HCT, 43 ± 2 %). These values remained constant during selective coronary hemodilution.

Discussion. The present study demonstrated that increases in coronary blood flow were sufficient to maintain myocardial oxygenation and function during hemodilution with perfusion pressure constant, but not during hemodilution with perfusion pressure reduced to simulate coronary insufficiency. Although reductions in blood viscosity apparently contribute to coronary hyperemia during hemodilution, this factor in itself could not raise flow adequately. The relative underperfusion of subendocardium during hemodilution with perfusion pressure reduced suggests that oxygen deficit may be magnified in this region. The present findings raise questions about use of isovolemic hemodilution clinically in patients with coronary artery disease.

References

1. Crystal GJ, Salem MR. Myocardial oxygenation during selective, graded coronary hemodilution in the working canine heart. Anesth Analg 1986; 65:S38

2. Crystal GJ, Khoury E. Effect of selective coronary hemodilution on myocardial reactive hyperemia. Fed Proc 1986; 45:533

3. Heymann MA, Payne BD, Hoffman JIE, and Rudolph AM. Blood flow measurements with radionuclide-labeled particles. Prog Cardiovas Dis 1977; 20:55

Table 1. Effects of Coronary Hemodilution

	HCT (%)	CBF (ml/min)	$C(A-V)O_2$ (vol. %)	MVO_2 (ml/min)	%SS	EPI/ENDO RATIO
NB	44	53	7.30	3.57	16.0	1.15
	± 2	± 11	± 1.35	± 0.63	± 2.0	± 0.10
HD	18*	146*	3.12*	3.73	14.5	1.30
	± 2	± 33	± 0.70	± 0.71	± 1.9	± 0.10
HD-CI	17*	48+	3.95*	1.68*+	9.6*+	0.73*+
	± 2	± 11	± 0.88	± 0.26	± 2.4	± 0.06

Mean ± S.E. * vs NB, + vs HD, P<0.05.

Supported by NIH Grant HL-33803

Title: IS PROPHYLACTIC DANTROLENE INDICATED FOR MHS PATIENTS UNDERGOING ELECTIVE SURGERY?

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Introduction: Prophylactic dantrolene (oral or intravenous) is recommended for malignant hyperthermia susceptible (MHS) patients undergoing elective surgery. However, the incidence of MH reactions and anesthetic complications in a large population of MHS patients who received a trigger-free anesthetic for elective surgery without prophylactic dantrolene is not known. To determine the incidence of these complications in MHS patients, we reviewed the anesthetic records of 956 MHS patients undergoing elective muscle biopsy.

Methods: We retrospectively reviewed the anesthetic management and peri-operative complications of 956 MHS patients undergoing elective muscle biopsy. The patients were referred for elective muscle biopsy because of a previous MH reaction, a family history of MH, or undiagnosed muscle cramps. We recorded the peri-operative complications in the operating room, recovery room, and on the ward post-operatively (Table). The criteria for positive muscle biopsy included a positive response to halothane contracture (normal = 0), caffeine contracture (normal > 4.1), and combined halothane and caffeine contracture (normal > 1.2). Statistical significance ($P < 0.05$) was determined using the Chi-squared test with Yates correction.

Results: Of the 956 patients (mean age 31.2 yrs, range 1-95), 643 were biopsy-positive and 313 were biopsy-negative. Regional anesthesia (spinal, epidural, and field block with tetracaine, lidocaine, and mepivicaine) was used in 6.3% of the patients. Those receiving general anesthesia (93.7%) were premedicated with oral diazepam and intramuscular pantopon. Neither oral nor intravenous dantrolene was given. General anesthesia was induced with intravenous diazepam, droperidol, and fentanyl, and maintained with nitrous oxide and oxygen after endotracheal intubation. Muscle relaxants were not used. All patients were monitored in a routine manner for MHS. In most cases, the vastus lateralis muscle was biopsied. Six patients (10%) receiving regional anesthesia had nausea, or pain at the biopsy site, whereas 127 patients (14.2%) receiving general anesthesia had minor complications (Table). There was no significant difference in the incidence of complications between regional and general anesthesia. Four patients who were muscle biopsy-positive (0.62%), developed mild MH reactions in the recovery room after general anesthesia: one was treated successfully with general measures, and the other three were treated successfully with intravenous dantrolene.

Discussion: The incidence of MH reactions in a large population of biopsy-positive MHS patients who receive a trigger-free anesthetic for minor elective surgery without prophylactic dantrolene (0.62%), is extremely small. The four minor MH reactions which did occur, occurred in the recovery room and were easily reversed with intravenous dantrolene. Most of the other minor complications (table) may be attributed to the avoidance of muscle relaxants during intubation and to the use of large doses of narcotics and anxiolytics during anesthesia. In view of the very low incidence of MH reactions in this high-risk (biopsy-positive) group of MHS patients who received a trigger-free anesthetic, and because intravenous dantrolene reverses MH reactions, prophylactic dantrolene is not indicated for MHS patients undergoing minor elective surgery.

References:

1. Wingard DW: Controversies regarding the prophylactic use of dantrolene for malignant hyperthermia. Anesthesiology 1983;58:489-90
2. Flewellen EH, Nelson TE, Jones WP, Arens JF, Wagner DL: Dantrolene dose response in awake man: implications for management in malignant hyperthermia. Anesthesiology 1983;59:275-80
3. Kolb ME, Horne ML, Martz R: Dantrolene in human malignant hyperthermia - a multicenter study. Anesthesiology 1982;56:254-62

Table

	OPERATING ROOM		RECOVERY ROOM		WARD	
Muscle Biopsy:	MH^+	MH^-	MH^+	MH^-	MH^+	MH^-
Complications:						
Respiratory-						
Difficult intubation:	12	8	--	--	--	--
Laryngospasm:	7	3	--	--	--	--
Bronchospasm:	3	1	--	1	--	1
Cyanosis:	--	--	1	--	--	--
Apnea:	--	--	1	1	--	--
Cardiovascular-						
Tachycardia:	1	1	3	1	1	--
Bradycardia:	2	--	2	1	--	--
Atrial fib.:	--	--	1	1	1	--
PVC:	5	2	7	2	1	--
Hypotension:	1	--	--	--	--	--
Temperature-						
Decrease:	1	--	4	--	--	--
Increase:	5	1	8	2	6	1
MH reactions-	--	--	4	--	--	--
Other-						
Nausea:			4	3	3	1
Vomiting:			1	1	3	1
Drowsiness:			11	12	1	1
Wound pain:			5	1	--	--

Title: EVALUATION OF PATIENTS WITH PULMONARY HYPERTENSION FOR ORTHOTOPIC HEART TRANSPLANTATION: NITROPRUSSIDE VS. NITROGLYCERIN

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Introduction: When patients with end-stage cardiomyopathies are evaluated for orthotopic heart transplantation (OHT), pulmonary hypertension (PH) responsive to vasodilator therapy may allow heart transplantation. However, primary or fixed PH unresponsive to vasodilator therapy mandates heart-lung transplantation. A major limiting factor when weaning from cardiopulmonary bypass (CPB) after OHT is right heart failure when the newly transplanted; ischemic heart is suddenly presented with elevated afterload i.e., pulmonary hypertension. The Stanford criteria for OHT requires pulmonary artery systolic (PAS) $\leq$ 50 mm Hg, pulmonary artery mean (PAM) $\leq$ 30 mm Hg, and pulmonary vascular resistance (PVR) $\leq$ 320 dyne . sec^{-1}. cm $^{-5}$ after infusion of sodium nitroprusside (SNP)^{1} . The purpose of this study was to evaluate and compare nitroglycerin (NTG) with SNP in these patients.

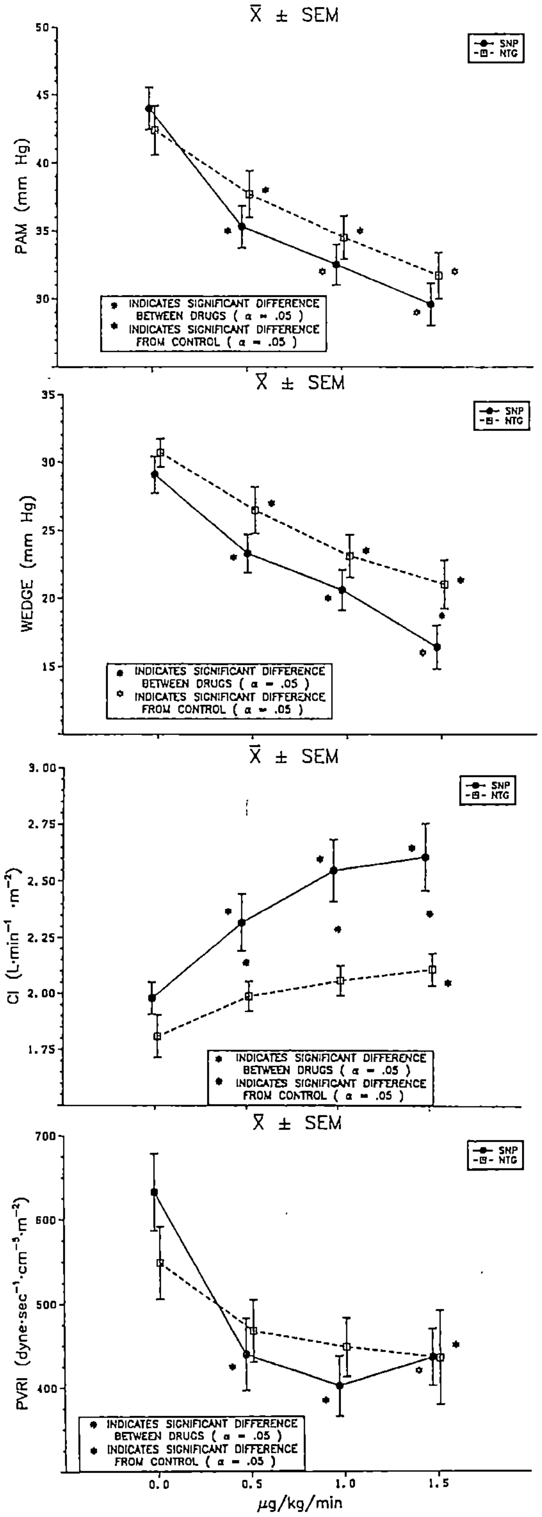
Methods: With the approval of the Human Investigation Committee and after informed written consent 24 patients with PH were cannulated with radial artery and thermodilution pulmonary artery catheters. Hemodynamic measurements and calculations were made after progressive infusions of SNP (0.0, 0.5, 1.0 and 1.5 ug.kg^{-1}) and then NTG (0.0, 0.5, 1.0, and 1.5 ug.kg^{-1}). All patients were at rest, without medication, normocarbic, normoxic and with normal pH. Analysis of variance and Tukey Pairwise comparison were used for data analysis.

Results: (See figures)

Discussion: Because the pulmonary circulation is distensible, and the pulsatile component of flow is great, the calculation of PVRI accounts only for 50-60% of impedance to flow for the right ventricle compared to SVRI accounting for greater than 90% of impedance to flow for the left ventricle. SNP and NTG equally reduced PVRI and PAM but the mechanism for the change was different. SNP caused a significantly greater increase in CI and greater decrease in PCWP than NTG. Even though PVRI is an inadequate index of right ventricular afterload, it is the only clinically available index. NTG at this dose level appears to lower PH to levels that match the Stanford SNP criteria and offers a therapeutic alternative.

References

1. Wyner J.: Personal Communication, 1986.



Title: TREATMENT OF PULMONARY HYPERTENSION AFTER HUMAN ORTHOTOPIC HEART TRANSPLANTATION

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Introduction: Even though patients may meet the Stanford[1] criteria for reduction in pulmonary hypertension (PH) after vasodilator therapy with sodium nitroprusside (SNP) or nitroglycerin (NTG), right heart failure after orthotopic heart transplantation (OHT) remains a significant cause of intraoperative mortality and postoperative morbidity. The Stanford criteria for OHT requires pulmonary artery systolic pressure < 50 mm Hg, pulmonary artery mean pressure $\leq$ 30 mm Hg, and pulmonary vascular resistance (PVR) $\leq$ 320 dyne . sec^{-1}. cm^{-5}. Some centers have used right ventricular assist devices after OHT when pharmacologic therapy has failed.

Methods: With the approval of the Human Investigation Committee and informed written consent, we documented our intraoperative treatment of 15 consecutive patients with PH that had been evaluated preoperatively with SNP and NTG and then underwent OHT.

Results: Inotropic and vasodilator therapy was required in nine patients prior to and during induction of anesthesia. Additional hemodynamic support with the intra-aortic balloon pump (IABP) was necessary preoperatively in four patients.

All patients were weaned from cardiopulmonary bypass (CPB) with isoproterenol at a minimal doses of 2 $ug.min^{-1}$. Ten patients (66%) required dobutamine and eight patients (53%) required epinephrine for inadequate cardiac index (< 2.0 L. min^{-1}. m^{-2}).

Isoproterenol caused sufficient pulmonary vasodilation that no additional vasodilators were required in four patients (27%). Six patients (40%) required one vasodilator (SNP or NTG) and five patients (33%) required both SNP and NTG. Two patients received prostaglandin E_1 (PGE) infusions in the right atrium and norepinephrine infusions in the left atrium for severe pulmonary hypertension and right ventricular failure unresponsive to massive doses of nitroglycerin, nitroprusside, phentolamine, and beta-agonists[2]. No additional IABP's were inserted. All patients were discharged from the hospital.

Discussion: We feel that rational anesthetic care including inotropic and vasodilator therapy is only possible with the use of thermodilution pulmonary artery catheters in contrast to other centers that only monitor CVP. These catheters, in long sterile sheaths, can be refloated after CPB. In patients with pulmonary hypertension, we initiate vasodilator therapy as soon as the PAM $\geq$ 15mm Hg, before terminating CPB, and attempt to prevent excessive right ventricular afterload and seek to avoid any right ventricular distension. A second vasodilator i.e, NTG, was added if the PAM $\geq$ 25 mm Hg after toxic levels of SNP i.e.$\geq$ 10 $ug.kg^{-1}$. min^{-1} were already infusing. PGE and norepinephrine provided dramatic responses in two patients who couldn't be weaned from CPB due to right heart failure. Even though the pulmonary pressures were not changed with the addition of the PGE, the systemic pressures were dramatically reduced requiring infusions of norepinephrine in the left atrium. Obvious right ventricular distension resolved with clinically apparent increased right ventricular contractility.

We also noted that patients with pulmonary hypertension do not tolerate alpha-agonist infusions and will develope severe pulmonary hypertension with low doses of epinephrine or norephinephrine when concomitant vasodilator therapy is absent.

The Stanford criteria is obviously at the upper limit of pulmonary hypertension that can receive OHT. We were able to wean all patients from CPB with these techniques and recommend this approach before the use of the right ventricular assist device.

References

1. Wyner J. Personal Communication, 1986.

2. D'Ambra M, et al: Prostaglandin E_1, JTCS 89:567-572, 1985.

Title: Onset and Recovery of Atracurium and Succinylcholine Blockade with Simultaneous Train-of-Four and Single Twitch Responses

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Introduction: Neuromuscular blockade is commonly monitored using either single twitch (ST) or train-of-four (TOF) stimulation. It is generally assumed that the response to the first twitch of TOF is similar to ST. Stimulation of nerves increases blood flow to corresponding muscle in animals (1) and the onset of neuromuscular blockade is also affected by muscle blood flow (2). Thus, it follows that the presence of stimulation, by itself, may be expected to accelerate the onset of neuromuscular blockade. The purpose of this study was to determine whether this effect may be present in the range of stimulation used clinically. This was tested, using patients as their own controls, by stimulating both ulnar nerves simultaneously with TOF and ST and comparing the responses of both adductor pollicis muscles.

Methods: After institutional approval, informed consent was obtained from adult ASA 1 & 2 patients. Anaesthesia was induced with thiopental and fentanyl, and maintained with nitrous oxide and fentanyl. Both ulnar nerves were stimulated and the force of contraction of both adductor pollicis muscles was recorded. The site of the intravenous line and the pattern of stimulation for each arm were randomized. Twenty-two patients had train-of-four (TOF) applied to one arm and single twitches (ST) to the other, and repeated every 12 seconds. After a 5-minute baseline recording, atracurium, 0.4 mg/kg or succinylcholine, 1 mg/kg, was injected rapidly. Onset time was taken as time from injection to 90% block of ST height or 90% block for the first-twitch height in a TOF. Recovery was defined as the time to spontaneous return to the same level. Results were expressed as mean ± SEM, and student's paired t test was used for statistical analysis.

Results: In all patients, and for both relaxants tested, the apparent onset of blockade was shorter when measured by TOF compared with ST stimulation (Table I and Fig. I). For atracurium, the time to 90% blockade of twitch height for TOF stimulation was 1.4 minutes shorter than that for ST. In all patients, the time to 10% recovery was longer for TOF compared with ST stimulation.

TABLE I

RELAXANT	ONSET (MIN)			RECOVERY (MIN)		
	ST	TOF	p	ST	TOF	p
Atra	3.4 ±0.4	2.0 ±0.2	.0005	31.2 ±1.4	35.0 ±1.1	.0003
Sux.	1.00 ±0.07	0.82 ±0.08	.0005	7.1 ±0.5	8.1 ±0.5	.001

Discussion: This study demonstrates that the pattern of stimulation can affect the apparent onset and recovery of blockade by depolarizing and non-depolarizing relaxants. The results are consistent with a contraction-induced increased delivery of the drug to the neuromuscular junction by TOF stimulation. Recovery from TOF stimulation occurs slightly later, presumably because of the larger amount of drug delivered to the muscle. Although statistically significant, the differences in recovery times achieved by ST and TOF stimulation are clinically insignificant. However, the mode of stimulation influences onset time markedly such that data obtained with different modes of stimulation should not be compared.

References:

(1) Saxena PR, Dhasmana KM, Prakash O. A comparison of systemic and regional hemodynamic effects of d-tubocurarine, pancuronium and vecuronium. Anesthesiology 59: 102-108, 1983

(2) Goat VA, Yeung ML., Blakeney C, Feldman SA. The effect of blood flow upon the activity of gallamine triethidodide. Br. J. Anaesth. 48: 69-73, 1976

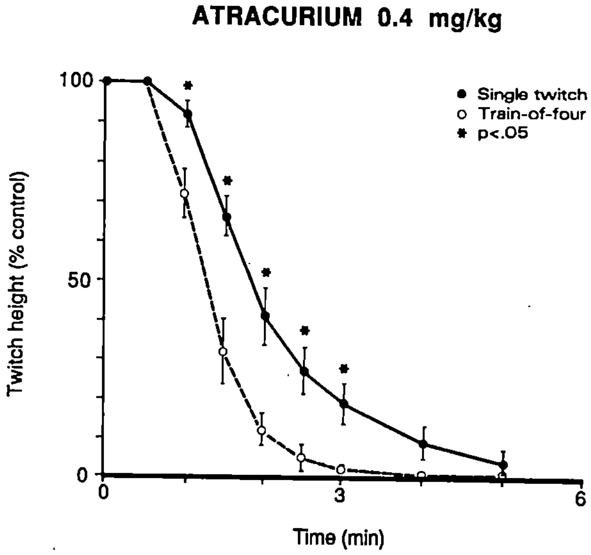

Figure 1. Single twitch height and height of first twitch of train-of-four during onset of atracurium neuromuscular block.

Title: IMPROVED CIRCULATION DURING HYPOTHERMIC CARDIOPULMONARY BYPASS (CPB) UTILIZING A PULSATILE DEVICE *

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It has been debated over the past 3 decades whether pulsatile flow offers superiority over continuous flow. Proponents of continuous flow argue that short CPB (2-3 hrs) offers very little advantage in return for the complexities associated with the pulsatile pump. In order to determine the adequacy of total body perfusion during the hypothermic state in humans, we studied oxygen consumption (OXC), serum lactate levels (SL), systemic vascular resistance (SVR) and mean arterial blood pressure (MBP) on pulsatile and non-pulsatile CPB.

METHODS: Twenty-four consenting adult patients undergoing elective aorto-coronary bypass surgery were randomly divided into 2 groups, Gr I, roller (N=13) and Gr II, pulsatile (N=11). Excluded from the study were emergency cases, those with left ventricular ejection fraction < 0.4 and those on either cardiac assist devices or intravenous vasoactive drug therapy which could affect the status of the peripheral vascular resistance. All patients were anesthetized in a similar fashion with diazepam (D) or midazolam (M), sufentanil (S), pancuronium (P) and xylocaine for induction and maintained on D or M, S, P and isoflurane. Additional D or M, S and P were administered just prior to commencement of CPB. No continuous infusions of vasoactive drugs were utilized on CPB. Pump flows were maintained at 2.5 $l/min/m^2$ during normothermia and 1.5 $l/min/m^2$ during hypothermia. MBP was kept between 40-70mmHg and pressures outside this range were treated with boluses of aramine or nitroglycerin as needed. Blood samples were obtained at 3 separate periods for OXC and SL. OXC was calculated by using the Fick principle. SL was measured using pyruvate to lactate Dupont automatic clinical analyzer at time 1 (t1) during normothermia prebypass, time 2 (t2) at the lowest temperature on CPB and time 3 (t3) upon stabilization off CPB. MBP was measured at t1, t2 and t3 and SVR was calculated using the established formula. Patients were cooled to blood temperature 28°C and warmed to rectal temperature of at least 36°C before discontinuation from CPB. Statistical analyses were performed using Student's t test for comparison within the 2 groups. P value < 0.05 was considered statistically significant.

RESULTS: Initial determination of control value (SVR, MBP, OXC and SL) between the 2 groups revealed no statistical difference. Patients were closely matched for age, number of aorto-coronary grafts performed, CPB time and aortic cross-clamp time (CCT) (Table 1). MBP was significantly lower with pulsatile pump at t2 (55±6 vs. 62±7mmHg) with corresponding reduction in SVR. Pump flows were statistically similar (Gr I = 1,654±176, Gr II = 1,709±197cc/min). SL levels were statistically lower in the pulsatile group at t2 (1.9±0.8 vs. 3.0±1.2 mmol/l). OXC was significantly higher in the pulsatile group at t2 (46±8 vs. 33±9 $cc/min/m^2$).

DISCUSSION: Total body oxygen consumption and SL levels would be considered among the leading indicators of the integrity of microcirculation. Should pulsatile flow be utilized routinely for short CPB such as the usual aorto-coronary bypass procedure? Our study indicates that tissue perfusion is better preserved with the pulsatile flow as evidenced by increased OXC and decreased SL during hypothermia on CPB. Since both MBP and SVR were significantly lower in the pulsatile group, we conclude that pulsatility helped to maintain patency of the peripheral vasculature and yielded these beneficial effects. Although we still do not have clear indication as to the clinical benefits of this finding, it is certainly appropriate to conclude that pulsatile flow was superior in this setting. Further investigative work to assess its clinical implications would be worthwhile.

Table 1 ROLLER Gr I vs. PULSATILE Gr II

	Gr I, N=13	Gr II, N=11	
Mean age (yrs)	63 ± 9.3	65 ± 8.2	NS
Pump time (min)	135 ± 35	138 ± 29	NS
CCT (min)	80 ± 24	77 ± 21	NS
Vessels	4.0 + 0.8	3.7 + 0.8	NS

	t1=prebypass		t2=coldest temp.	
	Gr I	Gr II	Gr I	Gr II
MBP(mmHg)	74+9.5	77+11.4	62+7.3	55+6.4 *
SVR (dynes-sec/cm^5	1297±341	1293±276	1642±348	1343±144 *
Rectal temp (c)	35.1±0.5	35.1±0.5	29.4±1.0	30.0±1.1
Flow rate $ml/min/m^2$	2154±445	2464±713	1654±176	1709±197

* = p=0.01

Fig. I - Roller vs. Pulsatile Flow-Oxygen Consumption

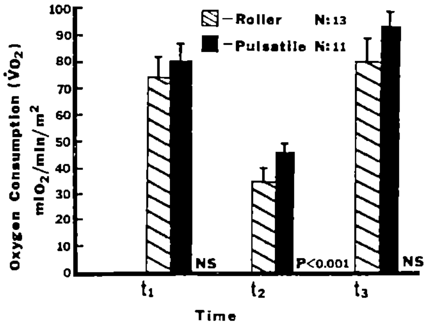
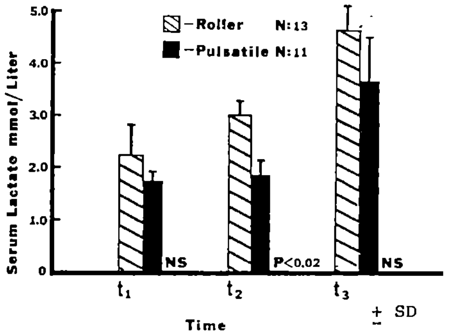


Fig. II-Roller vs. Pulsatile Flow - Serum Lactate



t1=prebypass, t2=coldest temp., t3=postbypass

Reference: Fox, L.W., Blackstone, E.H., Kirlin, J.W. Relationship of whole body oxygen consumption to perfusion flow rate during hypothermic cardiopulmonary bypass. J Thorac Cardiovasc. 83:239, 1982.

*Electro-Catheter Corporation

Title: PERFORMANCE OF INJECTOR-TYPE VAPORIZER DURING HIGH-FREQUENCY POSITIVE PRESSURE VENTILATION

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Introduction. High-frequency positive pressure ventilation (HFPPV) is used in extracorporeal shock-wave lithotripsy and certain neurosurgical and thoracic operations to minimize movement at and around the surgical field. Various depths of anesthesia are required for these procedures and therefore precise control over delivery of volatile anesthetic agents is highly desirable. With high-frequency jet ventilation (HFJV), anesthetic gas can be entrained from a circle system, however, delivery to the patient is variable and inefficient (1). The Siemens Servo Ventilator (900D) has the capability to provide HFPPV and to control rate and volume of ventilation precisely. Combined with a N_2O/air/O_2 mixer and an in-line, injector-type vaporizer, the system can be used to deliver anesthetic gas mixtures. A previous study has shown the effects of positive pressure ventilation and of flow rate on anesthetic delivery by some variable bypass vaporizers (2). We examined the effects of rate and ventilatory minute volume on performance of an injector-type vaporizer used with conventional and high-frequency ventilation.

Materials and Methods. The Siemens Servo Ventilator 900D with a manual ventilation accessory, N_2O/air/O_2 mixer, and isoflurane vaporizer 952 was used. A low compliance breathing circuit was attached and connected via a 7.5-mm endotracheal tube to a test lung with a mixing fan and a gas sampling port in the bellows compartment. Compliance of the test lung was set at 0.1 L/cm H_2O and the gas mixer was set to deliver 100% O_2. Minute volumes of 5, 15, 20, and 25 L/min; and vaporizer settings of 0.5, 1.0, 2.0, and 3.0% were studied. For each minute volume, the vaporizer setting was varied incrementally from 0.5–3.0%. At each vaporizer setting, the ventilator rate was increased to 10, 33, 66, 100, and 115 breaths/min. At each rate, the concentration of anesthetic delivered was measured with a Perkin-Elmer mass spectrometer (MGA-1100), which sampled gas from the test lung after equilibration at each combination of settings. The test lung was flushed with 100% O_2 after each measurement and each measurement was repeated three times. Statistical analysis was performed by ANOVA.

Results. Mean deviations in volume of gas delivered from the gas volume setting in volume percent were 0.20, 0.15, 0.125, 0.11, and 0.11 for the rates of 10, 33, 66, 100, and 115 breaths/min, respectively (Fig. 1). Statistical analysis showed the rates of 10 and 33 breaths/min to be significantly different from all the other rates ($P < 0.01$). The mean deviations in volume percent were 0.11, 0.10, 0.14, and 0.24 for minute volumes of 5, 15, 20, and 25 L/min, respectively. Analysis of variance indicated that the mean deviations from the set concentration at minute volumes of 20 and 25 L/min were significantly greater than those at all other minute volumes studied ($P < 0.01$);

Discussion. Despite a calibration offset, the vaporizer delivered consistent concentrations of anesthetic over a wide range of ventilator settings. While the difference in vaporizer accuracy during conventional rates (10 and 33 breaths/min) compared with high rates (≥ 60 breaths/min) is statistically significant, the range of the mean deviations is only 0.09 volume percent and is not clinically significant. Likewise, the observed increase in vaporizer output at the higher minute volumes we studied is also of minimal clinical significance because the range of the mean deviations was only 0.14 volume percent. Vaporizer performance may deviate significantly at higher minute volumes than we studied. The Siemens injector-type vaporizer enables the clinician to deliver volatile anesthetic agents during either conventional or high-frequency (HFPPV) ventilation.

Reference

1. Gravenstein N, Weber W, Banner MJ. Entrainment of anesthetic gases from the circle system during high frequency jet ventilation and anesthesia. (Abstr) Anesthesiology 1986; in press.
2. Lowe HJ, Beckham LM, Han YH, Evers JL. Vaporizer performance: closed circuit fluothane anesthesia. Anesth Analg 1962; 41:742-54.

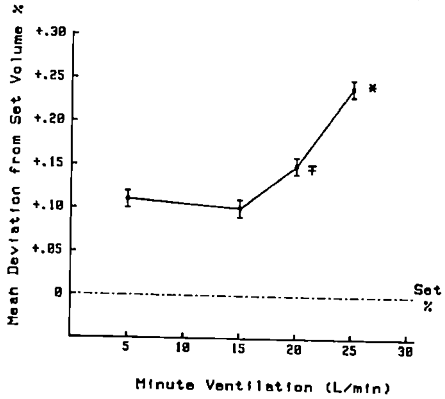

Figure 1. Effect of minute ventilation on vaporizer output. Each data point represents mean ± SD of pooled data ($N = 60$) for all vaporizer and ventilator rate settings. *$P < 0.01$ compared with all other minute ventilations. ‡$P < 0.01$ compared with all other minute ventilations.

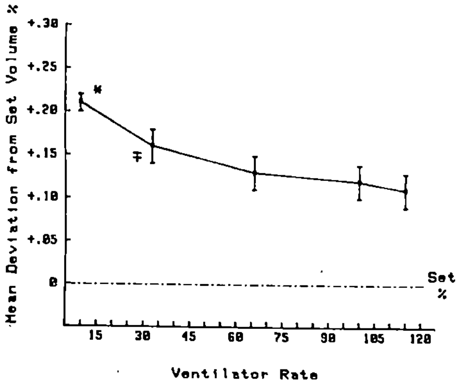

Figure 2. Effect of ventilator rate (breaths/min) on vaporizer output. Each data point represents mean ± SD pooled data ($N = 48$) for all vaporizer and minute ventilation settings. *$P < 0.01$ compared with all other ventilatory rates. ‡$P < 0.01$ compared with all other ventilator rates.

Title:

NAUSEA AND VOMITING AFTER OUTPATIENT ANESTHESIA — EFFECTIVENESS OF DROPERIDOL ALONE AND IN COMBINATION WITH METOCLOPRAMIDE

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Introduction. Nausea and vomiting is a common complication following outpatient anesthesia. The antiemetic effectiveness of low-dose droperidol is controversial (1,2). Metoclopramide, a gastrokinetic agent, has been reported to be a highly effective antiemetic by some investigators (3,4), while others have questioned its ability to prevent postoperative nausea and vomiting (1). We determined the incidence of postoperative nausea and vomiting when droperidol was administered alone or in combination with metoclopramide prior to outpatient anesthesia. In addition, we assessed the effect of nausea and vomiting on recovery times following brief outpatient procedures.

Methods. One-hundred and eighty (180) consenting young women undergoing elective midtrimester abortion procedures under general anesthesia were studied. The study was approved by the Human Subject's Committee. Premedication consisted of droperidol (0.5-1.0 mg iv), administered 3-6 minutes prior to induction of anesthesia, alone or in combination with metoclopramide (10-20 mg iv) administered 15-30 min prior to the droperidol. Anesthesia consisted of sufentanil 10-20 µg, followed by induction of anesthesia with either thiopental (3-4 mg/kg) or methohexital (1-1.5 mg/kg). Maintenance of anesthesia consisted of a thiopental (8-16 mg/min) or methohexital (3-6 mg/min) infusion in combination with nitrous oxide (N_2O), 70% in oxygen. Three different anesthetic techniques were studied: Group I received thiopental for induction and maintenance; Group II received thiopental for induction and methohexital for maintenance; and Group III received methohexital for both induction and maintenance. The patients were allowed to breathe spontaneously and a stable level of anesthesia was maintained by varying the rate of the maintenance infusion in response to clinical signs. At the end of surgery, the hypnotic infusion was discontinued. Recovery times from discontinuation of N_2O until awakening (eye opening), orientation (to person and place), ambulation (without assistance) and discharge (from the recovery room) were recorded. All episodes of nausea and/or vomiting were recorded by the recovery room staff. Data are reported as mean values ± S.D. Statistical analyses included Chi-squared test, Student's t-test and Mann-Whitney rank sum test, with $p<0.05$ considered statistically significant.

Results. The three anesthetic groups were comparable with respect to age (25±8 yr), weight (62±11 kg) and duration of anesthesia (19±5 min). Although there was no difference among the three anesthetic groups with respect to the incidence of nausea and vomiting (table 1), less postoperative nausea and vomiting was reported in the groups premedicated with the combination of droperidol and metoclopramide (versus droperidol alone). Nausea and/or vomiting prolonged the time to ambulation and discharge following brief outpatient procedures (table 2). In Group III, the ambulation and discharge times for the droperidol-treated patients (77±32min and 102±35min, respectively) were significantly longer than for those patients receiving the droperidol-metoclopramide combination (61±[illegible]min and 82±23min, respectively), $p<0.05$.

Discussion. Previous studies involving outpatients undergoing similar gynecologic procedures have reported a 41-68% incidence of postoperative nausea and vomiting depending on the type of premedication (1,5). Our data are consistent with studies demonstrating the limited effectiveness of low-dose droperidol for antiemetic prophylaxis in patients undergoing outpatient anesthesia (1,2,5). Although higher doses of droperidol are more effective (6,7), residual sedation can itself delay discharge from an outpatient unit. In our study, a combination of droperidol and metoclopramide was more effective in preventing nausea and vomiting than droperidol alone. One possible explanation may relate to a synergistic action between the gastrokinetic medication, metoclopramide, and the centrally-acting drug, droperidol. Since the occurrence of nausea and vomiting significantly prolonged the recovery room stay for these outpatients, the antiemetic effect of a droperidol-metoclopramide combination would be of advantage in busy ambulatory surgery centers where rapid recovery is important.

References.

1. Cohen SE, Woods WA and Wyner J. Anesthesiology 1984; 60:67-69.
2. Valanne J and Korttila K. Acta Anaesthesiol Scand 1985; 29:359-362.
3. Clark MM and Storrs JA. Br J Anaesth 1969; 41:890-893.
4. Ho TLK, Suseela M and El-Etr AA. Anesth Analg 1984; 63:264.
5. White PF, Coe V, Shafer A, Sung ML. Anesthesiology 1986; 64:99-106.
6. Mortensen PT. Acta Anaesthesiol Scand 1982; 26:48-52.
7. Abramowitz MD, Oh TH, Epstein BS et al. Anesthesiology 1983; 59:579-583.

Table 1: Incidence of postoperative nausea and/or vomiting after outpatient anesthesia

Anesthetic technique	N	Droperidol	N	Droperidol plus metoclopramide
Group I	50	44%	20	20%
Group II	30	33%	30	17%
Group III	30	37%	20	20%
OVERALL	110	39%	70	19%*

*Significantly different from droperidol, $p<0.05$

Table 2: Effects of postoperative nausea and vomiting on recovery times (min)

	No Symptoms	Nausea	Nausea+Vomit
Number	124	12	44
Awakening	3±2	3±1	3±2
Orientation	4±2	4±2	3±3
Ambulation	64±16	88±34*	95±38*
Discharge	83±20	115±35*	120±37*

*Significantly different from asymptomatic group, $p<0.05$.

Title: SYNERGY BETWEEN THE ANTINOCICEPTIVE EFFECTS OF INTRATHECAL CLONIDINE AND SYSTEMIC MORPHINE IN THE RAT

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Introduction. Intrathecal administration of alpha-2 adrenergic agonists has been shown to produce analgesia in various animal models, as well as in humans.[1] However, the clinical utility of this analgesic effect is limited by side effects; notably hypotension, bradycardia and disturbance of motor function. One strategy to circumvent this problem is to use other pharmacological agents to selectively potentiate the analgesic effect. Such potentiation occurs with the co-administration of intrathecal alpha-2 adrenergic agonists and intrathecal morphine.[2] However, whether systemic morphine is capable of producing a similar potentiation has never been addressed. This information is particularly relevant since the antinociceptive action of supraspinal morphine is partly mediated through the release of norepinephrine at the spinal cord level.[3] This study was performed to test whether combined administration of subtherapeutic dose of intrathecal clonidine (an alpha-2 adrenergic agonist) and a subtherapeutic dose systemic morphine can produce analgesia.

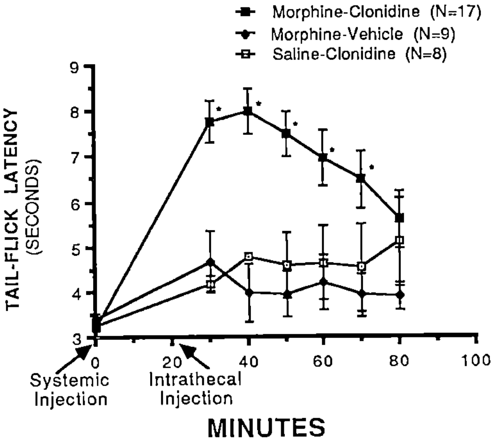
Methods. Thirty four male Sprague-Dawley rats (250-350g) were anesthetized with sodium pentobarbital (60 mg/kg i.p.) to permit intrathecal insertion of a PE-10 tubing catheter to the caudal portion of the lumbar enlargement. Animals were allowed to recover for at least 5 days before being tested. The tail-flick (TF) test was used to assess analgesia. The heat source was a a projection lamp which was focussed on the tail, with latency to movement as the endpoint. The heat was turned off at 9 seconds if there had been no response (cut-off), and this value was assigned as the response latency. In the first set of experiments the animals received either morphine sulfate (1 mg/kg s.c.) dissolved in saline, or an equal volume of saline alone, administered in a blinded fashion. Twenty minutes later 5 µg of clonidine HCl in 5 µl of a balanced salt solution (BSS) was administered intrathecally. In the second set of experiments all animals received morphine sulfate (1 mg/kg s.c.), followed by a blinded intrathecal injection of either 5 µg of clonidine HCl or 5 µl of BSS. Measurements of tail-flick latency were made prior to drug administration, and then every ten minutes, beginning ten minutes after the intrathecal injection. Response latencies after drug administration were converted to percent maximal possible effect (%MMPE), where %MPE = [(postdrug latency - baseline latency)/(cut-off - baseline latency)] X 100%. Data were evaluated for significance using a Mann-Whitney U test with a $P < 0.05$ considered significant.

Results. Response latencies following s.c. morphine plus intrathecal vehicle, or s.c. saline plus intrathecal clonidine were not significantly different from baseline. However, the combination of s.c. morphine plus intrathecal clonidine produced significant analgesia. This effect was apparent at 10 minutes and persisted for 50 minutes.

Discussion. Systemic morphine produces analgesia by activating opiate sensitive sites in the spinal cord and the brainstem.[4] Activation of brainstem sites, in turn, produce inhibition of spinal pain transmission via descending pathways to the spinal cord. There is evidence supporting a role of several neurotransmitters, including norepinephrine, as the spinal cord mediators of this descending modulatory system. The results of the present experiments demonstrate a greater than additive effect following the combined administration of systemic morphine and intrathecal clonidine. This effect could result solely from an interaction between clonidine's spinal alpha-2 adrenergic effect, and a direct action of systemic morphine at spinal opiate receptors. Alternatively, the observed synergistic effect may depend on an action by systemic morphine at opiate sensitive sites in the brainstem causing the activation of descending noradrenergic pathways. Selective potentiation of analgesia is possible under these circumstances because release of norepinephrine is restricted to the pain-modulating noradrenergic neurons activated by morphine. Work is now underway to establish the relative contribution of these elements to the observed effect.

References.

1. Coombs DW, Saunders RL, Lachance D, Savage S, Ragnarsson TS, Jensen LE. Intrathecal morphine tolerance: Use of intrathecal clonidine, DADLE, and intraventricular morphine. Anesthesiology 1985;62:358-363
2. Yaksh TL, and Reddy SVR. Studies in the primate on the analgesic effects associated with intrathecal actions of opiates, alpha-adrenergic agonists and baclofen. Anesthesiology 1981; 54:451-467
3. Yaksh TL. Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing. Pharmacol-Biochem-Behav. 1985; 22:845-58
4. Fields HL. Neural mechanisms of opiate analgesia. In: Fields HL et al.,ed. Advances in Pain Research and Therapy, Vol.9. New York: Raven Press, 1985:479-486



Data for mean tail-flick latency. (+/- SEM) *p<0.05

TITLE: THE EFFECT OF HYPERGLYCEMIA ON NEUROLOGIC OUTCOME FOLLOWING SPINAL CORD ISCHEMIA IN THE RABBIT

AUTHORS: JC Drummond, M.D., SS Moore, B.S., JA Zivin, M.D., Ph.D., HM Shapiro, M.D.

AFFILIATION: The Departments of Anesthesiology (Neuroanesthesia Research) and Neurology, the University of California, San Diego and the Veterans' Administration Medical Center, La Jolla, California

INTRODUCTION: While there is evidence that an elevated serum glucose (SG) prior to an episode of cerebral ischemia may result in a worsened post-ischemic cerebral metabolic state[1] and a poorer neurologic outcome[2], there have been no comparable investigations of spinal cord ischemia. This study was undertaken to determine whether moderate hyperglycemia present at the onset of spinal cord ischemia influences the incidence or severity of the subsequent neurologic deficit.

METHODS: Spinal cord ischemia in the New Zealand White Rabbit (NZWR) was produced by balloon occlusion of the abdominal aorta.

ED_{50} Determination. The ED_{50} for the aortic occlusion duration required to cause paraplegia was determined by the method of Zivin[3,4]. Thirty-two fasted (18 hr) NZWRs, wieght 2.9-3.2 kg, were anesthetized with halothane in O_2 by mask. A 4 Fr balloon tipped angiography catheter was placed transfemorally in the aorta with the tip 0.5-1.5 cm distal to the left renal artery. The anesthetic was discontinued and after a 2 hr recovery period, the aorta was occluded by balloon inflation. Occlusion was confirmed by the cessation of pulsatile distal pressure. Occlusion durations ranged from 7.5 to 30 min. The catheter was removed immediately post deocclusion. Neurologic function was graded by a blinded observer daily for 3 days. Rabbits were scored as paraglegic (paraplegic or paraparetic and unable to hop) or non paraplegic (normal or paretic and able to hop). The ED_{50} was determined by quantal analysis[3,4].

Dextrose Study. Twenty-four fasted NZWR's were studied. Preparation was as above. Fifteen minutes prior to aortic occlusion, 14 animals received a slow iv bolus of 50% dextrose (0.5 g/kg) and 10 received normal saline. All occlusions were for 14 minutes (the ED_{50} for paraplegia). Neurologic scoring was performed for three days. The incidence of paraplegia in the two groups was compared with Fisher's exact test.

RESULTS: ED50 The ED_{50} for paraplegia on Day 3 was an occlusion of 13.99 ± 2.67 (SE) mins. Only 2 rabbits changed status between neurologic evaluations on Days 1 and 3 (1 became paraplegic and 1 became non-paraplegic).

Dextrose Study. Dextrose administration resulted in a significantly (p<.004) higher pre-occlusion SG in the dextrose group than in control animals (291±82 vs 166±67 mg/dl). However, the immediate post occlusion SG did not differ between the 2 groups (207±70 vs 173±76 mg/dl). Cardiovascular and biochemistry data are given in the Table. There were no significant between groups differences in blood pressure, heart rate, blood gases, hematocrit or osmolarity (freeze point depression). There were four post occlusion deaths in the dextrose group. Two died after seizure-like activity between 2 and 3 hours post occlusion and 2 were sacrificed to relieve distress following similar events. There were no such occurrences among control animals. Four of 10 animals in the control group and 10 of 10 in the dextrose group were paraplegic on Day 3. The difference was significant (p=.004).

DISCUSSION: These data indicate that moderate elevation of SG prior to and during a period of spinal cord ischemia in NZWRs is associated with a markedly poorer neurologic outcome. This difference does not appear to be explained by differences in osmolarity, cardiovascular function, or systemic acid-base parameters. However, it has been suggested[1] (though there is not uniform agreement[5]) that the adverse effect of an elevated SG is the result of increased lactate production during and/or after the period of ischemia. The explanation for the seizure-like activity which we observed is obscure.

Given that moderate intraoperative elevation of SG is not uncommon, these results may have implications for the anesthetic management of patients undergoing procedures which entail risk of spinal cord ischemia. In particular, it is possible that dextrose containing intravenous fliuds should be administered for specific indications rather than as a matter of routine.

REFERENCES:
1. Siemkowicz et al., Acta Physiol Scand 110:22[illegible]-232, 1980.
2. Pulsinelli et al., Am J Med 74:540-544, 1983.
3. Waud DR, J Pharm Exp Ther 183:577-607, 1972.
4. Zivin et al., Arch Neurol 39:408-412, 1982.
5. Welsh et al., J Cereb Blood Flow Metab 3:486-492, 1983.

	CONTROL				DEXTROSE				CTRL vs DEXTROSE
	PRE SALINE	PRE OCCLUSION	POST OCCLUSION		PRE DEXTROSE	PRE OCCLUSION	POST OCCLUSION		
MAP(mmHg)	97±16	97±17	83±17	ns	9[illegible]±6	93±9	96±18	ns	ns
HR (b/m)	232±28	237±20	258±27	ns	230±10	226±38	283±24	*p<.03	ns
pH	7.43±.06	7.44±.05	7.42±.07	ns	7.46±.05	7.48±.05	7.47±.05	ns	ns
PCO2(mmHg)	31±2	29±3	23±3	*p<.001	3[illegible]±7	27±5	20±6	p<.002	ns
PO2(mmHg)	86±8	89±11	95±7	ns	8[illegible]±9	90±5	97±7	ns	ns
BD(meq/l)	2±4	4±3	8±4	*p<.002	[illegible]±4	2±4	6±5	*p<.006	ns
HCT(%)	40±5	40±5	42±5	ns	3[illegible]±5	39±3	41±4	ns	ns
GLUC(mg/dl)	168±50	166±67	173±66	ns	137±15	291±82	207±70	*p<.04	#p<.004
OSM(mOsm/l)	293±15	292±16	295±15	ns	289±[illegible]2	294±14	297±16	ns	ns

TABLE. Mean arterial pressure (MAP), heart rate (HR), blood gas, base deficit (BD), hematocrit (HCT), blood glucose (GLUC), and osmolarity (OSM) data prior to administration of 0.5 g/kg of dextrose (DEXTROSE) or saline (CONTROL), prior to aortic occlusion, and immediately post aortic deocclusion. * indicates a significant (p<.05) within group difference (repeated measures analysis of variance). # indicates a significant between groups difference (unpaired t test). All values are mean ± SD.

Title: PHARMACOKINETICS OF ALFENTANIL CONTINUOUS I.V. INFUSION IN NEUROSURGICAL PATIENTS

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Introduction. Because of its unique pharmacokinetic and dynamic properties among I.V. narcotic agents, Alfentanil has been found to be most suitable for continuous I.V. administration[1,2]. However, a report of post operative respiratory depression has suggested the possibility of either a rebound increase in plasma concentration (Cp) or cumulative effects[4]. In the present study, we have used Alfentanil at a fixed dosage and rate of administration, both for induction (bolus) and maintenance (infusion) of general anesthesia in neurosurgical patients. Two standard dose regimens were used and the pharmacokinetic behavior of the drug analyzed.

Methods. After approval from our Institutional Review Board, 11 patients (age 18-60, ASA physical status I or II), scheduled for craniotomy, gave their consent for the study. They were free of renal, hepatic or cardiac disease. Valium (10ug/70kg) for premedication and droperidol (50ug/kg) just before induction were given to all patients. Alfentanil was administered following two randomized protocols: in group I, 200 ug/kg bolus for induction and 1 ug/kg/min infusion for maintenance; in group II, 150 ug/kg bolus for induction and 1.5 ug/kg/min infusion for maintenance - the constant rate infusion, started during induction, was stopped about 1 hour prior to the end of surgery. Other anesthetic drugs used were: N_2O, pancuronium, and Isoflurane (.25% to .5%) whenever necessary. In addition to routine clinical observation, cardiovascular stability, extubation criteria and recovery scores were closely examined. Alfentanil arterial plasma samples were taken before and after induction, during the period of infusion, and up to 6 hours after the end of the infusion. Alfentanil Cps were determined by radioimmunossay. Volumes of distribution at steady state (Vdss), fitted curves computed for a two-compartment model, terminal elimination half lives (t 1/2 B) and plasma clearances (Cl) were determined for each patient and for each group of patients. The values between the 2 groups were compared by Student's t test.

Results. Group I included 5 patients and Group II 6 patients. Both were comparable in age, weight, height and clinical status. The mean duration of Alfentanil infusion was 202 minutes (SEM: ±32 min). During the time of infusion (up to 7 hours), there was no evidence of Cp build up over time in either group. Also, Alfentanil Cps were not significantly different between groups during the infusion steady state. At the end of the infusion, a bi-exponential curve was found to provide a good fit for the drug elimination data in all patients (see fig. 1). The calculated pharmacokinetic variables for both groups of patients are summarized on Table I.
In 6 patients out of 11, no Alfentanil could be detected after 3 hours following the end of infusion (level of detection, 10ug/ml). A delayed temporary increase in Cp during the elimination phase was found in 2 patients (at 15 min and 60 min). "End-of-Surgery-to-extubation" time was: 11.5 ± 3.2 min. Although all patients were drowsy in the postoperative period, measured clinical respiratory parameters (rate, TV, $ETCO_2$) were normal.

Discussion. The lack of evidence of drug accumulation during infusion with either drug regimen would tend to make the dosage used clinically acceptable in these patients. Differences in pharmacokinetic variables between the 2 groups never reached significance for this limited number of patients. The pharmacokinetic parameters found are comparable to previous reports, and in spite of relatively large individual variations, there has been no evidence of delayed elimination following the prolonged administration of Alfentanil. A transient Cp increase in 2 patients, within 1 hour following the end of infusion, has been the only noted abnormality. These pharmacokinetic findings have been fully supported by the incidental clinical findings of the recovery period.

References.
1. Stanski D, et al: Anesthesiology, 57:435-438, 1982.
2. Fragen RJ, et al: Br J Anaesth 55:1077-1081, 1982.
3. Sebel PS, et al: Br Med J 289:1581-1582, 1984.
4. Shafer A, et al: Anesthesiology 63:A283, 1985.

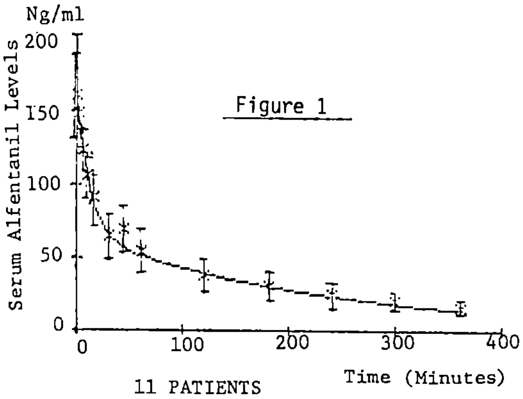

Figure 1

11 PATIENTS
(means ± SEM)

Patients	t ½ β(min) (mean ± SD)	Vdss(L/kg) (mean ± SD)	Cl(ml/kg/min) (mean ± SD)
Group I	86 min(± 32)	1.07(±.36)	8.49(±3.91)
Group II	91 min(±41)	1.41(±.63)	11.41(±5.63)

(No statistically significant differences between the 2 groups)

TABLE I

Title: LUMBAR VERSUS THORACIC CONTINUOUS EPIDURAL SUFENTANIL FOR POSTOPERATIVE ANALGESIA AFTER UPPER ABDOMINAL SURGERY

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Introduction. Continuous infusion of epidural narcotics is an effective means of providing postoperative analgesia.(1-3) While highly lipid-soluble narcotics may be unlikely to migrate in cerebrospinal fluid (CSF) and cause delayed respiratory depression, this same property may limit the extent of analgesia. In this study we compared the analgesic efficacy of a continuous infusion of sufentanil when administered from lumbar or thoracic epidural catheters after upper abdominal surgery.

Methods. This study was approved by our committee on human studies, and informed consent was obtained in each case. Twenty-four patients for abdominal surgery requiring incisions above the level of the tenth thoracic dermatome were studied. On the morning of surgery, patients were randomly assigned to one of three groups: Group I patients had epidural catheters placed at a spinal level at the midpoint of the anticipated incision; Group II and Group III patients had catheters inserted at the L2/3 or L3/4 interspace. All patients received an isoflurane based anesthetic. One hour prior to the conclusion of surgery each patient received an epidural injection of 50 ug. of sufentanil diluted in saline to 10cc. At the conclusion of surgery, an infusion of sufentanil was begun: Group I and Group II patients received sufentanil 2.5 ug/cc at a rate of 4 cc/hr; Group III patients received sufentanil 1.25 ug/cc at 8 cc/hr. Patients who complained of pain received an epidural bolus of sufentanil 25 ug. in 10 cc., and the infusion was increased 25%. If a patient complained of pain within four hours after these interventions, they were removed from the study. Patients who were somnolent but comfortable had their infusions decreased by 25%. Catheters were removed 48 hours postoperatively, or earlier if the patient was transferred, if analgesia was inadequate, or if the catheter malfunctioned. Every four hours from 0700 to 2300 each day a blinded observed asked the patient to take a deep breath, and then to assign their pain to a numeric score (0=NO PAIN, 10=WORST PAIN.) Side effects were recorded. Data were analyzed using analysis of variance and Fisher's Exact Test. Data are presented as mean ± S.D.

Results. The three groups of eight patients were comparable in age (overall, 57 ± 17 yrs.), height (67 ± 4 cm.), and weight (68 ± 19 kg). The mean duration of catheter placement was 33 ± 15 hours in Group I, 29 ± 18 hr. in Group II, and 40 ± 13 hr. in Group III. Table I compares the pain scores over the course of the study among groups. Two patients in Group I, three patients in Group II and one patient in Group III were removed from the study because of insuffient analgesia. Table II compares the hourly sufentanil dose among groups: Group II patients required more sufentanil and a wider range of infusion rates than Group III. This finding persisted even after excluding treatment failures. No group differences were seen in side effects: Three of 24 patients experienced respiratory rates < 10, three of 24 complained of pruritus, and one of 24 complained of nausea during the course of the study. Four of 24 were markedly somnolent in the immediate postanesthetic period.

Discussion. Previous investigators using continuous epidural infusions of fentanyl for postoperative pain relief have used thoracic epidural catheters to treat pain from upper abdominal incisions (1-3). Our study with sufentanil indicates that lumbar placement can be just as effective as thoracic, particularly when a high volume infusion is used. The reasons for this are probably related to the increased spread of epidurally administered solutions in this older population, possible CSF migration of this dose of sufentanil, and central analgesic effects of the epidurally administered drug.(4)

Conclusion. Acceptable postoperative analgesia can be obtained for a majority of patients undergoing upper abdominal surgery using an infusion of sufentanil 10 to 12 ug/hr. into the thoracic or lumbar epidural space. A higher volume infusion from the lumbar epidural space may be more efficacious, since volume and spread of solution may be an important factor with this opiate.

References.

1. Bailey PW, Smith BE. Continuous epidural infusion of fentanyl for postoperative analgesia. Anaesthesia 34:1006-1007, 1980.
2. Welchew EA, Thornton JA. Continuous thoracic epidural fentanyl. Anaesthesia 37:309-316, 1982.
3. Welchew EA. The optimum concentration for epidural fentanyl. Anaesthesia 38:1037-1041, 1983.
4. Colpaert Fc, Leysen JE, Michiels M. van den Hoogen RHWM. Epidural and intravenous sufentanil in the rat: Analgesia, opiate receptor binding and drug concentrations in plasma and brain. Anesthesiology 65:41-49, 1986.

TABLE I: COMPARISON OF POSTOPERATIVE PAIN SCORES FOR PATIENTS RECEIVING EPIDURAL SUFENTANIL INFUSION. (MEAN ± S.D.)

	HOURS AFTER INITIAL SUFENTANIL BOLUS			
	0 - 6	6 - 12	12 - 24	24 - 48
	GROUP I			
PAIN SCORE	3 ± 2	3 ± 2	2 ± 3 (n = 6)	1 ± 1 (n = 5)
	GROUP II			
PAIN SCORE	5 ± 2	5 ± 3	2 ± 2 (n = 6)	2 ± 2 (n = 4)
	GROUP III			
PAIN SCORE	4 ± 3	4 ± 3	3 ± 2 (n = 7)	2 ± 1 (n = 7)
SIGNIFICANCE	NS	NS	NS	NS

TABLE II: COMPARISON OF HOURLY SUFENTANIL DOSE REQUIREMENTS OF ALL PATIENTS AND OF PATIENTS WHO RECEIVED ADEQUATE ANALGESIA WITH THE CONTINUOUS EPIDURAL INFUSION. (MEAN ± S.D.)

	ALL PATIENTS		PATIENTS WITH ADEQUATE ANALGESIA	
	# OF PATIENTS	UG/HR	# OF PATIENTS	UG/HR
GROUP I	8	12 ± 3	6	11 ± 1
GROUP II	8	14 ± 3 *	5	13 ± 2 *
GROUP III	8	11 ± 2	7	10 ± 1

* = SIGNIFICANT DIFFERENCE FROM GROUP III, p < 0.04

Title: AFTER EPIDURAL NARCOTICS - WHAT NEXT FOR CANCER PAIN CONTROL ?

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Introduction. The augmentation of cancer pain control by epidural narcotics has been well established. Coombs(1) and others(2) have described drug tolerance, where we have suggested increasing nociceptive stimulation and a maximum epidural narcotic analgesia effect as limiting factors in achieving total pain control(3). When nerve root and bone pain overcome the analgesic effects of epidural narcotics, and neurosurgical or nerve ablative procedures are ineffective, can we consider using infusion of local anesthetic agents at home? Are the risks of such procedures outweighed by the benefits, and is such a technique ethical?
We will present a number of patients who have been managed at home on constant infusions of morphine and local anesthetic agents, and will discuss the legal problems, logistical problems, and patient family acceptance.

Methods. Eight patients with permanently implanted silicone-rubber epidural catheters, (modified Broviac catheters) achieved pain relief with epidural narcotics until nociceptive stimulation from bone or nerve pain required added analgesia. These patients were treated with constant epidural infusion of morphine and bupivacaine. The dose was calculated using the last successful twenty-four hour dose of epidural morphine divided into hourly doses with 0.125% bupivacaine and 1:400,000 epinephrine, infused at 6 ml per hour. The morphine and bupivacaine concentrations were adjusted according to pain complaints, where the volume was dictated by the required dermatome spread obtained from epidurograms(3). Constant infusion was obtained using a small Pharmacia programmable pump or the larger Autosyringe 5C pump. Family members and visiting nurses were instructed in drug preparation and pump use.

Results. Out of one-hundred and five patients treated for intractable cancer pain with epidural narcotic analgesia through permanent epidural catheters, eight received local anesthesic infusions (six at home). Infusion concentrations of bupivacaine varied from 0.125% to 0.5% and morphine doses from 6 to 15 mg per hour. In no cases was sedation a problem and the somatic and sympathetic blockade did not result in any significant changes. In three cases patients were able to ambulate to the extent of walking around the room, however in most cases their terminal state dictated bedrest. There was no 24-hour nursing support nor vital sign monitoring by family members.

Discussion. When epidural narcotic analgesia is nolonger effective in controlling bone and nerve root pain, the addition of local anesthetic analgesia is an effective means of controlling pain. This route of administration, when used chronically at low concentrations, may be administrated at home without the usual requirement for monitoring.
In some states nurses are legally restricted from injecting local anesthetic agents into the epidural space, this requires instructing family members in these techniques. Instruction, supplies, and equipment are provided by our nutritional support service.
None of the six home-care patients experienced any complications with the technique, and all but two died quietly at home from tumor-related complications. Two patients were admitted for terminal care at the families request.
Therefore, this technique should be considered for both hospitalized and home-care of the terminal patient who no longer achieves the desired pain relief from epidural narcotic analgesia alone.

References.

1. Coombs DW, Saunders RL, Gaylor MS, Block AR, Colton T, Harbaugh R, Pageau MG: Relief of Continuous Chronic Pain by Intraspinal Narcotics via an Implanted Reservior. JAMA 250:2336-2339, 1983.
2. Malone BT, Beye R, Walker J: Management Of Pain in The Terminally Ill By Administration Of Epidural Narcotics. Cancer 55:438-440, 1985.
3. Du Pen SL, Larson C, Omoto M, Ramsey D: Epidurogram Guide To Catheter Placement And Narcotic Dose-volume, In Cancer Patients With Thoracic Pain. Paper presented, American Society of Regional Anesthesia, San Antonio, Texas, 1985.

Title: AORTIC BLOOD FLOW ACCELERATION MEASURED BY DOPPLER ULTRASOUND AS AN INDEX OF CONTRACTILITY IN PIGS

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Introduction. The noninvasive evaluation of hemodynamic status is now possible with doppler ultrasound (DUS) using either transcutaneous (suprasternal) or esophageal probes linked with a microcomputer. Cardiac output determinations with this technique have been shown to correlate closely with those obtained by thermodilution (TD) in medical and surgical patients (1,2). Application of this method is limited to patients free of valvular heart disease and arrhythmias. It does, however, provide a continuous measurement of several hemodynamic parameters and avoids the complications associated with invasive monitoring. In addition to cardiac output, blood flow acceleration can be easily obtained with a microcomputer. Previous studies in dogs instrumented with electromagnetic flow probes suggested that maximal blood flow acceleration (Max-Acc) may be a sensitive index of myocardial contractility. The present study was designed to examine the relationship between contractility measured directly in situ to Max-Acc as determined by DUS.

Methods. Pigs weighing 40-50 pounds were anesthetized with pentothal 20 mg/kg, intubated and maintained on halothane, oxygen, and pavulon. End tidal halothane concentrations were maintained at 1±.1% with a Perkins-Elmer mass spectrometer and an Ohio vaporizer. Ventilation was set to maintain PCO_2 at 40±2 mmHg. An 8.5 Fr introducer was placed in the right internal jugular vein and a 7 Fr Gould thermodilution catheter was passed into the pulmonary artery. A 20 g teflon catheter was placed in the right carotid artery for measurement of arterial pressure. The heart was exposed by a left thoracotomy. A 20 g teflon catheter was placed into the left ventricle at the apex for measurement of left ventricular pressure. A Walton-Brody strain gauge was sewn onto the left ventricle for measurement of tension development. The first derivatives of ventricular pressure (dP/dt) and tension (dT/dt) development were obtained electronically. A L-3000 cardiac output monitor with research software (Lawrence Medical Systems, Seattle, WA) was used to measure cardiac output and Max-Acc. This unit uses microprocessors to analyze the ultrasonic doppler shift frequencies from the esophageal probe to compute cardiac output and Max-Acc as the average of 6 consecutive cardiac cycles. The data from 8-12 serial determinations was averaged to determine each DUS data point shown. The unit was initially calibrated in each experiment to the mean of five TD cardiac output determinations. After control values were obtained, dopamine was titrated to increase dP/dt approximately 25, 50 and 75%. Each time dP/dt stabilized, hemodynamic measurements were repeated. Values are expressed as a percent of change from control. Correlation coefficients were obtained by a linear regression analysis.

Results. Cardiac index determinations were similar by the two methods (figure 1). Cardiac index (TD) increased from 4.6 ± .32 L/min/sq M to 6.46 ± .3 L/min/sq M in response to dopamine 7-20 µg/kg/min. Max-Acc, dP/dt and dT/dt all increased in response to dopamine. Max-Acc increased from a control value of 1.77 ± .2 m/sec^2 to 2.65 ± .27 m/sec^2. There was a positive correlation between changes in Max-Acc and dP/dt (.848; figure 2) and Max-Acc and dT/dt (.768; data not shown).

Discussion. The close correlation of Max-Acc with directly measured indices of myocardial contractility reported here provides evidence that this noninvasively-derived parameter may be very useful in monitoring for myocardial failure during anesthesia. The transesophageal DUS method not only avoids the complications of invasive monitoring, but provides a measure of contractility not supplied by a pulmonary artery catheter. Prior to this, left ventricular function could only be estimated utilizing pulmonary artery occlusion pressure and cardiac outputs to derive parameters of ventricular work. These had to be plotted against an index of filling pressure and repeated frequently to follow trends. This approach may be circumvented in the future by continuous monitoring of Max-Acc by DUS. However, further studies are required to determine the usefulness of following Max-Acc as an index myocardial function and the accuracy of this parameter in the presence of different anesthetic agents and pathophysiological states.

References.

1. Huntsman LL, Stewart DK, Barnes SR, et al. Noninvasive doppler determination of cardiac output in man. Circ 1983; 593.
2. Freund RR, Padarich CA. A comparison of cardiac output techniques: transesophageal doppler versus thermodilution cardiac output during general anesthesia in man. Anesth 1985; 63:A191.
3. Noble MI, Trenchard D and Guz A. Measurement and significance of the maximum acceleration of blood from the left ventricle. Cir Res 1966; 19:139.

Fig.1 Cardiac Index by TD and DUS

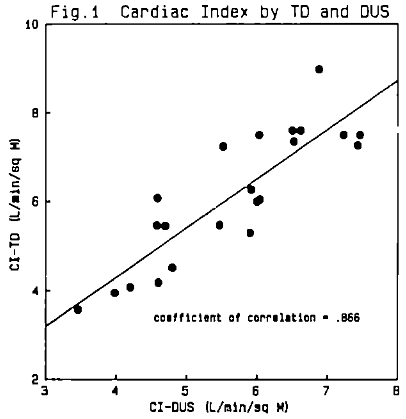
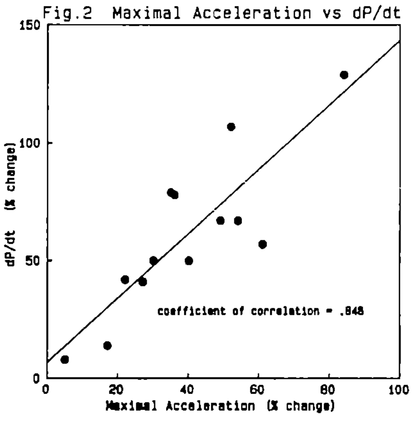


Fig.2 Maximal Acceleration vs dP/dt



Title: MATERNAL-FETAL DISTRIBUTION OF MEPERIDINE AND ALFENTANIL DURING LABOR IN THE RHESUS MONKEY

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Introduction. In order to prevent fetal depression, analgesics which have minimal maternal-fetal transfer are to be preferred for administration during labor. This study compares maternal-fetal transfer of meperidine, a commonly used labor analgesic with that of alfentanil, a newly developed agent not yet in use in obstetric practice. Meperidine is a phenylpiperidine analgesic with potency one-tenth that of morphine; alfentanil is a related synthetic opioid with potency ten times that of morphine. In addition to a higher potency, alfentanil is more highly protein bound than meperidine (92% vs 60%) and has a more rapid onset and briefer duration of action. These characteristics would be anticipated to reduce placental transfer of alfentanil.

Methods. Labor was induced in nine conscious, chair restrained rhesus monkeys with oxytocin. The animals were monitored for heart rate, blood pressure, respiratory rate and contractions throughout labor. Progress of labor was observed via vaginal exam and when membranes entered the cervical canal they were ruptured. At this time drug was administered and labor was followed to vaginal delivery. Four animals received 2 mg/kg meperidine via intravenous catheter as a bolus injection. Five monkeys received alfentanil at a total dose of 0.1 mg/kg as an intravenous infusion over a one hour period. Two-three ml blood samples were drawn from dam and neonate at 0, 2, 12 and 24 hours post-delivery (the neonatal 0 time point sample was drawn from the cord). Blood samples were immediately centrifuged and frozen for subsequent analysis. Meperidine was analyzed by gas chromatography/mass spectrometry (1) and alfentanil by radioimmunoassay using antibody provided by the manufacturer (Janssen Pharmaceutica).

Results. Drug to delivery intervals ranged from 1.9 to 2.7 hours for meperidine and 1.8 to 3.7 hours for alfentanil. Fetal-maternal ratios averaged .47 ± .01 (mean ± SEM) at birth for meperidine and .26 ± .03 for alfentanil ($t = 5.63$, $p < .01$). Maternal plasma alfentanil concentrations decreased more rapidly in the postpartum period than did those of meperidine; maternal plasma levels had decreased an average of 79 + 5% for alfentanil versus 48 + 2% for meperidine at the two hour time point. Similarly, all 5 alfentanil treated fetuses had > 90% decrease in plasma levels from birth to two hours, while two of the four meperidine fetuses showed a > 90% decrease with the other two showing decreases of 43 and 25%.

Discussion. Plasma concentrations of alfentanil measured after birth suggest that this opiate analgesic is transferred less readily to the fetus during labor in the nonhuman primate than is the commonly used analgesic meperidine. This finding is in agreement with earlier studies of maternal-fetal distribution of opiate analgesics in the near-term rhesus monkey (2). The relative analgesic effectiveness of the two drugs was not determined in this experiment. However, the data suggest that pharmacokinetic considerations may eventually be of value in selecting safer and more effective analgesics for use during labor.

References.

1. Kuhnert BR, Kuhnert PM, Philipson EH, et al. Disposition of meperidine and normeperidine following multiple doses during labor. II. Fetus and neonate. Amer J Obstet Gynecol 1985;151:410-418.
2. Golub MS, Eisele JH, Jr, Anderson JH. Maternal-fetal distribution of morphine and alfentanil in near-term sheep and rhesus monkeys. Dev Pharmacol Ther 1986;9:12-20.

Supported by GM32920 and CR00169.

Title: EFFECT OF DIRECTION OF CATHETER INSERTION ON THE QUALITY OF OBSTETRIC EPIDURAL ANALGESIA

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Introduction. Women in labor with lumbar epidural analgesia often complain of sacral pain which is difficult to alleviate. Double catheter techniques have been described by Cleland (1) and others which are useful with perineal pain during the second stage of labor; these might alleviate refractory sacral pain, but would carry increased risk of dural puncture, intravascular injection, and local infection. Lumbar epidural with caudal direction of the catheter and non-selective (T10 - S5) block is practiced in many centers (2). Because of the frequency of complaints of sacral or rectal discomfort, we undertook a prospective study to determine the effect of direction of catheter insertion on sacral pain.

Methods. With approval by the Committee on Conduct of Human Research, 102 women were enrolled in the study. Using standard techniques, a 17 gauge Weiss needle was introduced into the epidural space at the L2-3 or L3-4 interspace, and a catheter was inserted 3 cm. The choice of rostral or caudal bevel orientation of the needle was left up to the individual placing the block. Analgesia was maintained in both groups with 0.25 - 0.375% bupivacaine, either by bolus or infusion. Five ml. top-up doses were provided in each group as needed. The women were questioned regarding sacral pain, and after parturition were asked to characterize the quality of the block. Statistical analysis was done using the chi-squared test, and $p < 0.05$ was considered significant.

Results. In all patients analgesia was obtained. An "excellent" block was obtained in 84% of the group with caudally directed catheters but only 51% of the group with rostrally directed catheters. ($p < 0.01$). Factors such as one-sided block, sacral pain, and missed segment, typically were cited by the woman in her decision to downgrade the quality of analgesia. No difference in incidence of one-sided blocks was seen. During the first stage of labor, sacral pain which was refractory to top-up doses was less common in the group with caudally directed catheters ($p < 0.01$). During the second stage of labor, sacral pain was also less common but there was no statistical difference.

Discussion. 1) A single caudally directed catheter is useful in decreasing the incidence of sacral discomfort during the first stage of labor. 2) It may also reduce the incidence of sacral discomfort during the second stage of labor. 3) It is rated by women labor as giving better quality pain relief.

References.

1. Cleland JGP: Continuous peridural and caudal block in obstetrics and surgery with postoperative analgesia. Anesth Analg 1952: 31:289-300.
2. Ostheimer, GW. Regional Anesthesia. In. Ostheimer, GW, ed. Manual of Obstetric Anesthesia. New York Churchill Livingstone, 1984:165-220.

Table.

	DIRECTION OF CATHETER INSERTION ROSTRAD (N=45)	CAUDAD (N=57)
Quality of analgesia		
None	0%	0%
Inadequate	9%	4%
Adequate	40%	12%
Excellent	51%	84% *
One-sided block	4%	2%
Sacral pain first stage	27%	5% *
Sacral pain second stage	20%	9% **

* $p < 0.01$, caudad vs. rostrad
** NS ($p = 0.10$), caudad vs. rostrad

Title: MASSIVE TRANSFUSION DURING ADULT AND PEDIATRIC LIVER TRANSPLANTS I: TRANSFUSION TECHNIQUE

Authors: JA Estrin, M.D., Ph.D., KG Belani, MBBS, MS, J Bushman, Ph.D., P Stock, M.D., A Karnavas, NL Ascher, M.D., Ph.D., JS Najarian, M.D., JJ Buckley, M.D.

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Introduction. Massive blood loss is a significant determinant of operative mortality during liver transplantation (1). Consequent massive transfusion is poorly tolerated by liver transplant recipients (2). The purpose of this report is to describe new transfusion technology to better manage blood loss during liver transplantation.

Methods. 45 adult and pediatric liver transplant recipients are the subjects of this report (14 adults, 40 ± 2 yrs, 61 ± 6 kg; 31 children 50 ± 6 months, 17± 3 kg). Indications for transplantation are listed in Table 1. Venous access was by percutaneous placement (right internal jugular vein) of a right atrial infusion line (children, 2.0 mm ID Hickman® catheter; adults, #18 French Bardic® cannula.) Monitoring included: a) arterial and pulmonary artery pressures b) urine output, c) temperature, d) ET CO_2, e) arterial and venous blood gases, Na^+, K^+, ionized Ca^{2+}, glucose every 30 minutes, e) Hct, Hgb, platelet count, fibrinogen, PT, PTT, and TT every hour, f) cardiac output (CO), pulmonary artery wedge pressure (PAWP), right atrial pressure (RAP) and standard derived parameters. Fluids included: a) infusion of D_5W (20 ± 5 mg/kg/hr of glucose), b) platelet concentrate, ≥ 4 ml/kg/hr and cryoprecipitate, ≥ 2 ml/kg/hr; to maintain a platelet count ≥ 250,000 and fibrinogen 0.4 gms/dl. c) replacement of blood loss with PRBC washed in saline and resuspended in FFP and Plasmalyte® to yield a Hct of 30 ± 2%. This "reprocessed blood" was filtered and placed in Harvey 1700® oxygenator reservoir for reoxygenation and rewarming to 37° C. Table 2 displays the effects of processing on the final composition of the blood infusate. The "reprocessed blood" was infused in aliquots, at rates which varied from 5 to 3,000 ml/min to maintain CO, PAWP, RAP at post-induction values and at hematocrit of 30%. Diuresis was induced to achieve serum K+ at ≤ 3 mEq/l. $CaCl_2$ was administered to maintain ionized Ca^{2+} at 1 ± 0.2 mM/l.

Results. Table 3 depicts CO, pH, urine output, Hct, temperature, K^+ values immediately following induction, at peak infusion rate (during liver flush) and immediately prior to abdominal closure. Table 2 depicts blood loss and infusion rates, extent of exchange transfusion, amount of blood component and crystalloid infusion. Perioperative mortality was 7% and 6% in adults and children, respectively. Perioperative mortality prior to the date of this technology was 61% (3).

Discussion. Large volume replacement at rapid rates during liver homotransplantation can be accomplished effectively with the technology described herein. Our data show that tissue perfusion, temperature, K, Hb, and pH can be maintained stable throughout this procedure. Perioperative mortality in this series is close to 10 fold lower than can be expected in similar patients (Results) managed with conventional techniques. This technology provides more effective prevention of hypovolemia, hypothermia and hyperkalemia.

Reference.
1. Butler P, et. al.: Blood transfusion during liver transplantation. Transfuion 23:433, 1983.
2. Fath JJ, et. al.: The effects of hyperdyanmic flow on lactate metabolism during hepatic transplantation: A requirement for aerobic metabolism in end stage cirrhosis. Critical Care Medicine 13(4):268, 1985.
3. Stock PG, Estrin JE, Fryd DS, Payne, WD, Belani KG, Elick BA, Najarian JS., Ascher NL: Factors influencing early survival following liver transplantation. Presented at American Society of Transplant Surgeons, Chicago, May 28-30, 1986.

Table 1
Indication for Liver Transplantation

E.H.B.A.	17	Hepatitis	5
P.B.C.	6	Scleros. Chol.	3
α-1 ATD	5	Wilson's	2
		Other	7

Table 2
Effects of Processing* on CPDA–1, Packed Red Cells

	BEFORE WASHING	AFTER WASHING	AFTER RESUSPENSION, REWARMING, AND REOXYGENATION
Hct (%)	76 ± 1	60 ± 1‡	35 ± 1‡
pH (units)	6.69 ± 0.1	6.74 ± 0.2‡	6.8 ± .03‡
PO_2 (torr)	20 ± 2	23 ± 2‡	361 ± 31‡
HCO_3^- (mEq/l)	14 ± 1	5 ± 1‡	3 ± 3‡
K^+ (mEq/l)	52 ± 4	8 ± 1‡	4.0 ± .3‡
Temp. (°C)	22°C	22°C	37°C

* Processing is saline washing, resuspension in FFP and Plasmalyte® rewarming and reoxygenation.

‡ p < .01 Significantly different from before washing

Table 3

	Post Induction	Peak infusion	Abdominal Closure
Hematocrit (%)	30 ± 1	30 ± 1	30 ± 1
Temperature (°C)	36 ± .2	36 ± .2	37 ± .3
Cardiac Output (L/min)	6.4 ± .7	4.7 ± .5*	6.6 ± 0.8
pHa (units)	7.42 ± 0.017	7.38 ± 0.016	7.47 ± 0.016
K^+ (mEq/L)	3.8 ± .10	2.7 ± .12*	2.9 ± .13*
Urine Output (total) (ml/kg/hr)		15. ± 2	
Urine Output (Anhepatic phase)		210 ± 36	

Significantly different from post induction (paired t-test) p < .01
Humoral, hematogical, acid-base and perfusion parameters during liver transplantation following induction, at peak infusion rate and at the end of surgery.

Supported by Anesthesia Research Fund

Title: EFFECTS OF HALOTHANE ON GLOBAL REVERSIBLE AND IRREVERSIBLE MYOCARDIAL ISCHEMIA

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Introduction. A model of canine regional myocardial ischemia (1) showed that halothane (H) decreases infarct size by 35%. This finding suggests some beneficial effect of H on stunned ischemic myocardial cells which fosters their recovery. If this effect results from an H-mediated increase in collateral coronary flow, it should not occur in a model of global myocardial ischemia without coronary collateral flow. This study tests that hypothesis.

Methods. Dogs anesthetized with α-Choloralose (AC) and gallamine were randomly assigned to one of two groups. Group I received additional AC, 10 mg/Kg q 30 min; Group II received 1.5 ± .2% H O_2, H concentration being varied to maintain a mean aortic pressue (MAP) of Group II animals equal to that of Group I. Both groups then underwent normothermic total cardiopulmonary bypass (TCPBP) (flow 120 ± 20 ml/kg, Hct 30 ± 5%). After 30 minutes on cardiopulmonary bypass, both groups were subjected to reversible (REV, n=6) and irreversible (IRRV, n=6) global ischemia (2) by cross-clamping the aorta for 20 or 60 minutes respectively, followed by one hour of reperfusion. Before, at the end of ischemia, and 10 and 20 minutes after reperfusion left ventricular myocardial biopsies were obtained for electron microscopy (EM) and for myocardial adenosine triphosphate (ATP) and creatinphosphate (CP) measurements (Lamprechts W. 1974); venous blood was also collected simultaneously from the venous limb of the oxygenator and the right ventricle for determination of total creatinphosphokinase (CPK) and CPK-MB isoenzymes (Yasmihneh, WG, 1985). Heart rate (HR), MAP, right atrial pressure (RAP), arterial blood gases (ABG) and temperature (T) were noted at each sampling time. Coronary perfusion pressure (CPP), and rate pressure product (RPP) were also recorded. Statistical comparisons of the data were made using paired or unpaired t-tests as indicated.

Results. For all dogs control CPP, RPP and PaO_2 were 59 ± 11 mmHg, 7529 ± 437 and 432 ± 41 mmHg respectively. There were no significant differences in CPP, RPP, and PaO_2 during ischemia and reperfusion between Group I and II. EM changes of IRRV ischemic dogs were more severe than those of REV ischemia; exposure to H did not cause ultrastructural differences. CPK-MB band isoenzyme levels (Fig. 1) (expressed as % of total CPK) show no changes in REV ischemia in Group I or II. In contrast the 10 and 20 min reperfusion CPK-MB release in IRRV ischemic dogs was significantly attenuated in the presence of H ($p < .01$). ATP values for IRRV ischemia declined (Fig 2), a trend to a lesser, but not significant, fall in ATP was only observed in IRRV Group II dogs (H). There was no attenuation of CP decline for REV and IRRV ischemic dogs treated with H.

Discussion. This data shows that H is capable of exerting a residual protective effect on ischemic myocardium (lesser enzyme release and a trend to conserve ATP) even when coronary collateral flow is not present. This residual beneficial effect of H may be explained by a direct cellular effect.

References.
1. Davis RF, et. al: The effect of halothane anesthesia on myocardial necrosis, hemodynamic performance, and regional myocardial blood flow in dogs following coronary artery occulsion. Anesthesiology 59:402-11, 1983.
2. Jennings RB, Ganot CE: Structural changes in myocardium during acute ischemia. Circ Res Suppl 3, 35:156-72, 1974.

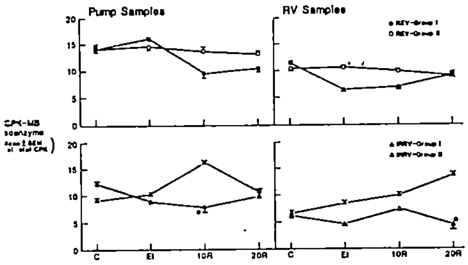

Figure 1 Effects of Halothane on CPK-MB Isoenzyme Blood Levels in Dogs with Reversible and Irreversible Ischemia. ✱ ($p < .05$ Unpaired t-test) Significantly Different from Group I. C=Control, E=End of Ischemia: 10R = Ten Minutes Reperfusion: 20R = 20 Minutes of Reperfusion

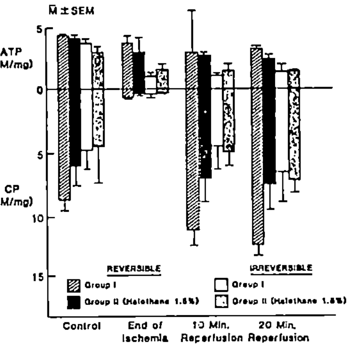

Figure 2: Changes In Myocardial ATP and CP During Global Reversible and Irreversible Ischemia

Supported in part by University of Minnestoa Graduate School Grant

Title: NITROUS OXIDE AUGMENTS THE CNS STIMULATION BY LAUDANOSINE IN RABBITS

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Introduction. Laudanosine, at plasma concentrations of up to 800 ng/ml, increases the minimum alveolar concentration (MAC) of halothane in rabbits by as much as 30% (1). Nitrous oxide, commonly combined with halothane to provide surgical anesthesia, may cause central nervous system (CNS) stimulation (2). In this study, we determined the combined effects of nitrous oxide and laudanosine on the MAC of halothane in rabbits.

Methods. Six non-fasting, unpremedicated New Zealand white rabbits were studied. Anesthesia was induced with halothane and oxygen via a mask, and tracheostomy was performed. Anesthesia was maintained with 1.0% inspired halothane in oxygen and ventilation was controlled to maintain P_aCO_2 at 35–40 mm Hg. Temperature was maintained with surface warming at 39°C. Carotid artery cannulation was done for blood pressure measurement and for sampling blood; an ear vein was cannulated for laudanosine administration. A unilateral fronto-occipital electroencephalogram (EEG) was obtained using subcutaneous needle electrodes. In all rabbits, the MAC of halothane was determined in duplicate during administration of 70% nitrous oxide (3). End-tidal halothane concentrations were measured using a Beckman LB-2 infrared analyzer. Laudanosine was then infused in all rabbits iv to consecutively reach 3 steady-state plasma concentrations of 200(I), 400(II) and 800(III) ng/ml by an infusion technique previously described (1). Blood samples were also obtained to confirm steady-state plasma laudanosine concentrations using a liquid chromatography analysis. Each steady-state plasma laudanosine level was maintained for at least 30 min and the MAC of halothane again determined in the presence of 70% nitrous oxide. Values for MAC of halothane of each of these steady-state plasma concentrations of laudanosine was compared to control by repeated measures analysis of variance and Dunnett's test (P 0.05). Results were also compared by t-test with a similar study done without nitrous oxide (1).

Results. The MAC of halothane increased in all rabbits above control values with infusion of laudanosine (Table 1). The mean percent (± SD) increases from control were 31 ± 11, 32 ± 18 and 43 ± 16% at 200, 400 and 800 ng/ml of laudanosine, respectively. However, these three values did not differ from each other. The results from a similar study without nitrous oxide were 8 ± 8, 22 ± 12 and 29 ± 19, respectively (1). Statistical comparison between the two studies showed a significant difference during the 200 ng/ml steady-state laudanosine infusion but not at 400 and 800 ng/ml. Plasma laudanosine determinations confirmed steady-state with close approximation to the expected concentrations of 193 ± 22, 443 ± 72 and 847 ± 67 ng/ml.

Discussion. This study suggests that nitrous oxide further increases the anesthetic requirement of halothane produced by laudanosine in rabbits, particularly at low plasma concentrations of laudanosine. Similar concentrations in the 100-200 ng/ml range for laudanosine have been measured in surgical patients after a single 0.5 mg/kg iv bolus of atracurium (3). Thus, use of nitrous oxide in patients receiving atracurium enhances laudanosine's potential to produce CNS stimulation. Our results point to the need for clinical studies of anesthetic requirement in surgical patients and also for further animal studies to determine the mechanism for the nitrous oxide and laudanosine interaction in augmenting the halothane MAC.

References.

1. Shi W-Z, Fahey MR, Fisher DM, Miller RD, Canfell C, Eger EI: Laudanosine (a metabolite of atracurium) increases the minimum alveolar concentration of halothane in rabbits. Anesthesiology 63:584-588, 1985

2. Harper MH, Winter PM, Johnson BH, Koblin DD, Eger EI: Withdrawal convulsions in mice following nitrous oxide. Anesth Analg 59:19-21, 1980

3. Fahey MR, Rupp SM, Fisher DM, Miller RD, Sharma M, Canfell C, Castagnoli K, Hennis PJ: The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. Anesthesiology 61:699-702, 1984

TABLE 1: MAC Values with Laudanosine*

Control	I	II	III
0.67	0.98(48)	1.04(57)	1.10(66)
0.91	1.10(20)	1.13(24)	1.17(28)
0.70	0.85(22)	0.87(24)	0.87(24)
0.76	0.96(27)	1.05(40)	1.17(55)
0.93	1.26(36)	1.28(38)	1.31(41)
0.74	0.99(34)	0.99(34)	1.04(41)
Mean %	31	32	43

* = values are end-tidal concentrations of halothane with % increase over control in parentheses

Title: A DOUBLE-BLIND COMPARISON OF OXYMORPHONE AND FENTANYL AS SUPPLEMENTS TO NITROUS OXIDE ANESTHESIA

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INTRODUCTION: Oxymorphone (Numorphan) is a semisynthetic opioid analgesic, which is about ten times as potent as morphine. Oxymorphone has seen limited use in anesthesia. Its effects on hemodynamics, and plasma histamine and immunoreactive beta endorphin levels have not been previously reported. We compared, in a double-blind study, these effects of oxymorphone with those of fentanyl during nitrous oxide-relaxant (balanced) anesthesia.

METHODS: Twenty consenting adult patients, scheduled for major orthopedic procedures, were randomly assigned to receive either oxymorphone (0.1mg/kg) or fentanyl (0.01mg/kg). The study was approved by the Human Studies Committee. The opioids were dispensed in identical syringes; each ml contained either 0.5mg of oxymorphone or 0.05mg of fentanyl. Oral diazepam (0.1mg/kg) was given 1 hour before anesthetic induction. The patients breathed oxygen via a face mask while intravascular catheters were inserted under local anesthesia. Pancuronium (0.02mg/kg) was administered to prevent rigidity. Following control hemodynamic measurements and arterial blood sampling, each patient received a rapid intravenous injection of 0.2ml/kg of opioid solution. Measurements and blood samples were obtained 2, 5, 30 and 60 minutes from start of injection. The patients were encouraged to breathe and report any subjective changes. After completion of the 5-minute measurement, anesthesia was induced with thiopental (4mg/kg) and endotracheal intubation facilitated with succinylcholine (1mg/kg). Anesthesia was maintained with $N_2O:O_2$ (3:2 L/min) and curare (0.4mg/kg). Ventilation was controlled mechanically. Additional increments of the study opioid were administered whenever systolic blood pressure and/or heart rate increased to greater than 15% over preanesthetic (control) values. Thiopental (0.5 - 1mg/kg) was given if the opioid drug failed to control these responses. Additional curare was given as judged by the response to peripheral nerve stimulation. Muscle relaxation was reversed with atropine (0.8 - 1.2mg) and neostigmine (2.5 - 5mg). Recovery times from discontinuation of N_2O to opening eyes on command, and to orientation to place and date were recorded. Hemodynamic measurements included cardiac output, (dye dilution), heart rate (ECG), and transduced intravascular pressures. Plasma histamine (control, 2 and 5 min) was measured by a radioenzymatic method and immunoreactive beta-endorphin (control, 30 and 60 min) by radioimmuno-assay.

RESULTS: The demographic data and baseline measurements were comparable in both groups. Neither drug altered hemodynamic variables or plasma histamine level after 2 and 5 min (Table). General anesthesia (30 and 60 min: no surgery) was associated with a reduction ($P < 0.05$) in hemodynamic variables in both groups; systemic vascular resistance did not change. Beta endorphin levels were not changed with fentanyl, but decreased ($P < 0.05$) from 49.2± 1[illegible]pg/ml (control) to 35.9 ± 9.7 and 34.6 ± 1[illegible]8pg/ml, 30 and 60 min, respectively, after oxymorphone. Duration of anesthesia (359 ± 43 min for oxymorphone; 370 ± 64 min for fentanyl) and recovery times were not different in both groups. Mean total dose requirements were 0.149 ± 0.007 mg/kg (10.65 ± 0.53 mg per patient) for oxymorphone and 0.02 ± 0.002 mg/kg. (1.59 ± 0.14 mg per patient) for fentanyl. Incremental doses were required at approximately similar intervals.

	CONTROL	p̄ 2 MIN	p̄ 5 MIN
	O/F	O/F	O/F
Cardiac	6.24/6.23	6.55/6.56	6.61/6.95
Output	±0.4/±0.5	±0.5/±0.6	±0.5/±0.5
Mean Art.	97/98	95/93	96/93
Pressure	±4/±3	±3/±4	±4/±4
Heart	77/74	76/72	77/76
Rate	±6/±5	±5/±5	±5/±5
Syst. Vas.	1243/1137	1153/1002	1171/975
Resist.	±100/±128	±104/±76	±140/±63
Histamine	311.7/303	195.6/198.6	211/140
(pg/ml)	±118/±124	±33.1/±33	±42/±16

Values are mean ± SE.O=Oxymorphone; F=Fentenyl

DISCUSSION: This double-blind study demonstrates that oxymorphone is a useful analgesic adjuvant to N_2O-relaxant anesthesia. Like fentanyl, it is associated with stable hemodynamics and no histamine release. In these aspects, oxymorphone differs from morphine. The surgical procedures were similar in both groups, i.e. a similar intraoperative "stimulus." Dose requirements (per kg) for comparable durations of anesthesia were seven and a half times more for oxymorphone (0.149 v. 0.02 mg/kg). This would be expected from their potencies relative to morphine.

Hemodynamic responses to laryngoscopy and intubation were suppressed by both drugs; responses to surgical incision were minimal. Postoperative nausea, vomiting and respiratory depression were similar.

Decreased beta-endorphin level with oxymorphone is interesting and deserves further study.

In summary, oxymorphone is an effective opioid analgesic supplement to nitrous oxide anesthesia, is associated with stable hemodynamics and no release of histamine. Its pharmacokinetic profile and use in high doses need to be examined.

Title : HAS NALBUPHINE A PLACE IN SEVERE PAIN?

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Introduction. Nalbuphine hydrochloride is a semi-synthetic agonist-antagonist opioid analgesic with a low potential to induce respiratory depression (1,2). Its analgesic potency has been reported as 0.5-0.9 that of morphine (3,4) and it has been used with some success in the management of pain after a variety of surgical procedures (3,4,). We report here a comparative study of the analgesic and sedative effects of nalbuphine and morphine in patients undergoing hip operations.

Method. Eighty patients scheduled for hip replacement, conforming to ASA grades 1 or 2 and not receiving opioid, sedative or anti-depressant therapy were studied. After informed consent, and following approval by the local Medical Ethical Research Committee, each received either nalbuphine (0.3 mg/kg) or morphine (0.15 mg/kg) by random allocation on a double-blind basis. One hour prior to operation each patient received premedication with 0.03 ml/kg I.M. of the coded drug. Anesthesia was standardized and consisted of thiopentone, pancuronium, isoflurane, and nitrous oxide (33%) in oxygen. Intraoperative opioids were not given. Arterial blood pressure, heart rate, and E.K.G. were monitored continuously throughout. Immediately postoperatively the residual analgesic effect was assessed by a trained nurse observer. As soon as a patient expressed a need for analgesia a second dose of the same coded drug was administered by the observer and additional assessments made at 30 minute intervals for two hours and at hourly intervals thereafter up to six hours. If analgesia proved unsatisfactory after the second injection, a third dose of coded drug could be given after a minimum of three hours. Inadequate pain relief within three hours of either postoperative injection was deemed "failed analgesia" and patients were given morphine intravenously to provide effective analgesia. Pain intensity was assessed by the patient as nil, moderate, or severe. Pain relief was assessed by the nurse observer and graded as slight, moderate, or complete.

Results. There were no significant differences in patients' age or weight but significantly more females received morphine than nalbuphine ($P < 0.05$ Fisher's Exact Test). Of the 80 patients studied, six of those receiving nalbuphine and eight of those receiving morphine requested no further analgesia during the study period. In contrast, analgesia "failed" in 10 of those who received nalbuphine compared with only two in the morphine group ($P<0.05$ Fisher's Exact Probability Test) (table 1). Table 2 shows that morphine reduced severe pain to a greater extent than nalbuphine at 60, 120, and 180 minutes ($P<0.05$ Mann-Whitney U test). Pain relief showed a similar trend in favour of morphine but the difference failed to reach significance at the 5% level.

Table 1. Number of patients in each group (n=40) requiring analgesia by the stated method.

	nil	postoperative IM 1	2	IV
morphine	8	22	8	2
nalbuphine	6	20	4	10

Table 2. Number of patients in the two treatment groups with intensity of pain graded at the times indicated (nalbuphine-N, n=34; morphine-M, n=32) (severe ++, moderate +, nil -)

minutes	0		60		120		180	
	N	M	N	M	N	M	N	M
++	34	32	16	5	15	4	14	5
+	0	0	14	24	12	15	14	15
-	0	0	4	3	7	13	6	12

Discussion. In this study of the analgesic effects of intermittent intramuscular nalbuphine and morphine, 78% of the eighty patients studied obtained moderate or complete pain relief after one hour. Morphine was 90% effective compared with 65% with nalbuphine. The quality of pain relief improved between one and two hours in the case of morphine so that after two hours 60% of patients had complete relief of pain. In contrast, only 38% of those who were given nalbuphine had complete pain relief two hours after administration. Despite allowing for a potency of only half that of morphine, we found that nalbuphine was significantly less successful than morphine in alleviating postoperative pain in this type of surgery.

References

1. Gal TJ, DiFazio CA, Moscicki J. Analgesic and respiratory depressant activity of nalbuphine: A comparison with morphine. Anesthesiology 1982;57:367
2. Romagnoli A, Keats AS. Ceiling effect for respiratory depression by nalbuphine. Clinical Pharmacology and Therapeutics 1980;27:478
3. Beaver WT, Feise GA. A comparison of the analgesic effect of intramuscular nalbuphine and morphine in patients with postoperative pain. Journal of Pharmacology and Experimental Therapeutics 1978;204:487
4. Bahar M, Rosen M, Vickers MD. Self-administered nalbuphine, morphine and pethidine. Anaesthesia 1985;40:529

TITLE: *AUTOTRANSFUSION AFTER CARDIAC SURGERY USING NEW APPARATUS: ALTERATION IN BLOOD AND PROTEINS*

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INTRODUCTION: *Hemorrhage, a major complication of cardiac surgery, has led to the development of autotransfusion apparatus (AA) for re-infusion of mediastinal shed blood (MSB) in an attempt to reduce the amount and risks of exogenous blood use. To evaluate concerns as to the quality of the MSB and its ability to reduce blood use*[1,2]*, we examined ease of use, technical problems, effectiveness, character of scavenged blood, and coagulation abnormalities associated with the use of the original Sorensen (S) and the more recently designed AA (Davol, Da; Deknatel, De) devices.*

METHODS: *With institutional approval and informed consent, 50 patients were studied after uneventful aortocoronary bypass using a membrane oxygenator, and a cell saver apparatus (Haemonetics). There were 11 controls (C) and 39 study (S) patients; 25 with De, 5 Da, 9 with the S-AA. The AA was connected in the OR just before transfer to the ICU. Samples were drawn: preoperatively, in the ICU on arrival, and 4 hours later both from the patient and chest tubing; and on postop days 1, 3 and 6. Studied were: ease of use, hemoglobin (Hgb), hematocrit (Hct), platelets (Plt); fibrinogen (FIB), fibrin split products (FSP); plasma free Hgb (PFH); red cell distribution width (RDW); prothrombin time (PT); partial thromboplastin time (PTT); bleeding volumes (BV); transfused volume (TV) of autologous and bank blood; and blood smears from patients, tubes and AA.*

RESULTS: *I. De and Da were simpler to use and more readily accepted than the older S-AA. II. BV in both study and control groups (Table 1) was similar at 4 (S 347±251 vs. C 160±160) and 24 hours (S 854±492 vs. C 603±284). Total use of blood products was also similar TV (S 2.1±2.2 and C 1.5±1.1). BV was > 700 ml at 4 hours in only 4 of the 50 patients (sub-group b). III. TV in sub-group b, 4.3±2.6 units was > than measured BV (1581±213), despite autologous re-infusion (AR) 977±194. TV was 0 in only one of sub-group B, who at 4 hours had BV of 700 and an equal volume of AR (700 ml). IV. Marked changes in cell and coagulation characteristics occurred; were similar in C and S patients; and were not affected by the type of AA (Da, De and S) used. Hct and Hgb of the MSB in the chest tubes on admission to the ICU and in the AA at 4 hours was 56 and 39% respectively of that of the patient (Table 2). MSB also showed no FIB; high levels of FSP, > 40 in all patients; and PFH increased 1305±1333% (Table 3). V. Smears of the blood in the AA showed normal RBC, no helmet or target cells; few WBC; and no Plts. Further, RDW was in the normal range in the patient and in MSB.*

DISCUSSION: *I. Mediastinal shed blood has a marked coagulopathy. Although this caused no apparent problems in this study, it might be a hazard if large volumes were infused. II. Re-infusing large amounts of plasma free hemoglobin may be undesirable.*[3] *III. RBC in the AA had a Hct of 12. Little actual salvage of blood occurred in the study, and autotransfusion had no effect on transfusion requirements. Only one patient among those with significant bleeding might have benefited from autotransfusion.*

TABLE I
HEMATOLOGIC CHANGES
CHANGES IN HEMOGLOBIN AND HEMATOCRIT

	ON ARRIVAL PATIENT	ON ARRIVAL TUBES	%PATIENT	SCAVENGER Set 4 hrs	%PATIENT 4 hrs	POD6
Hgb.s	1[illegible].6±1.5	6.1±1.8	58±17	4.2±1.7	40±16	10±1.2
.c	1[illegible].4±1.6	5.7±1.6	55±14	x	n/a	8.6±2.
.b	9 6±1.8	6.1±1.3	66±19	5.3±1.0	57±14	8.5±0.
Hct.s	3[illegible]±4	17±5	56±18	x	39±17	29±3
.c	3[illegible]±4	16±5	54±14	x	n/a	25±9
.b	2[illegible]±[illegible]	18±4	65±19	15±3	57±14	27±3

OTHER HEMATOLOGICAL CHANGES

		ICU ON ARRIVAL PATIENT	ICU ON ARRIVAL CHEST TUBE	ICU 4 HRS PATIENT	ICU 4 HRS SCAV SET	POD 1
Plts	.s	1[illegible]9±50	0	157±51	0	147±66
	.c	1[illegible]9±54	0	177±57	0	149±46
	.b	116±28	0	129±17	0	154±42
RDW	.s	1[illegible].7±1	13.4±2.5	13.9±1.2	14.0±1.2	x
	.c	1[illegible].6±1	13.6±1	13.8±0.8	n/a	x
	.b	14.6±2	14.9±2.7	15±2.2	14.6±2.2	x
PFH	.s	2[illegible]±44	296±157	8±9	228±131	x
	.c	1[illegible]±12	284±198	6±6	n/a	x
	.b	2[illegible]±34	109±59	3±1	119±86	x
FIB	.s	167±45	0	177±54	0	290±74
	.c	165±57	0	193±60	0	300±55
	.b	118±23	0	100±56	0	247±85
PT	.s	1[illegible].8±2.3	>40	15.1±3	>40	13.2±1
	.c	14.1±1.6	>40	15±1.3	>40	13.4±0
	.b	17±1	>40	20±7.2	>40	14±1.3
PTT	.s	30.2±6.7	>100	32±12	>100	26±3.8
	.c	27.2±6.7	>100	28±5	>100	25.6±2
	.b	3[illegible]±4	>100	40±20	>100	27±2

FIBRIN DEGRADATION PRODUCTS

	<10	10-40	>40
ON ARRIVAL	26	22	2
ICU 4 HRS	29	19	2
POD 6	16	26	6

TABLE 2
TRANSFUSION VOLUMES

	Transfusion OR	Bleeding 4 hrs	Aut Tr Vol	Total Transfused
Deknatel	0.6±0.8	376±296	381±318	2.2±2.5
Davol	1.2±1.6	268±118	198±192	2.8±2.1
Sorenson	0.2±0.4	305±134	326±231	1.3±1.1
Group	0.6±0.9	347±252	345±292	2.1±2.2
Control	0.5±0.8	x	n/a	1.5±1.1
Bleeding Group	0.5±0.9	955±216	977±194	4.3±2.6

REFERENCES:

1. *Popovsky MA, Devine PA, Taswell HF Intraoperative autologous autotransfusion. Mayo Clinic Proc 60: 125-134, 1985.*
2. *Thurer RL, Lytle BW, Cosgrove DM and Loop FD: Autotransfusion following cardiac operations: a randomized, prospective study. Ann Thor Surg 27: 500, 1979.*
3. *Weinberg ED: Iron and susceptibility to infectious disease. Science 215: 691, 1974.*

Title: A COMPARISON OF CONTINUOUS EPIDURAL NARCOTIC/LOCAL ANESTHETIC MIXTURES FOR POST-OPERATIVE ANALGESIA

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Introduction: The search for optimal postoperative pain control has yet to produce a safe and reliable technique. In an effort to improve upon parenteral narcotic use in the early postoperative period, spinal and epidural opiate analgesia has been investigated. Effective control of acute and chronic pain with epidural morphine was described by Behar in 1979.(1) However, in many clinical settings the use of spinal and epidural narcotics are not accepted because of associated respiratory depression, pruritis, nausea, and urinary retention.

Reports have appeared documenting superior analgesia from continuous epidural combinations of fentanyl/bupivacaine or morphine/bupivacaine in post-thoracotomy and labor patients.(2,3,4) The analgesia achieved was more profound in quality and duration than with narcotics or local anesthetics alone. Also, smaller total doses of narcotic and local anesthetic in combination appear to be efficacious, perhaps due to a synergestic analgesic effect. No patients in these studies suffered respiratory depression, although pruritis and nausea were not uncommon in patients given epidural narcotics.

No direct comparison of continuous epidural morphine/bupivacaine and fentanyl/bupivacaine for post cesarean section pain has been undertaken. The purpose of this study was to compare in a randomized double blind fashion continuous epidural fentanyl/bupivacaine versus morphine/bupivacaine for post cesarean section analgesia.

Methods: The study was approved by the Hospital Human Investigation Committee. Informed consent was obtained from 20 ASA status I and II obstetrical patients scheduled to undergo cesarean sections. Patients were prospectively randomized in blocks of four to one arm of the study group in a double-blind fashion. Lumbar epidural catheters were placed using Pharmaseal 17 gauge Touhy epidural needles (loss of resistance technique). Confirmation of correct catheter placement was made by demonstration of an epidural block to the fourth thoracic dematone adequate for cesarean section. All patients had epidural anesthesia for cesarean section provided by lidocaine 2% with epinephrine 1:200,000. Following surgery the patient received a bolus of 5 cc and then a continuous epidural infusion at 5 cc/hr of either fentanyl .001%/bupivacaine 0.1% (Group A), or MSO_4 .01%/bupivacaine 0.1% (Group B). Patients were allowed meperidine 50-75 mg and hydroxyzine 25-50 mg for additional pain relief per request.

The epidural catheter was maintained for a period of 24 hours. Assessments were made at the time of arrival into the recovery area and every four hours during the 24 hour period. Data collected consisted of degree of pain according to a linear analog scale, the number and amount of supplemental narcotic doses, pruritis if present, nausea, vomiting, and somnolence. The results of the pain scores were analyzed by two-way anova with one measure repeated. The number of narcotic doses and incidence of pruritis, nausea, vomiting and somnolence were analyzed using Fisher's Exact Test for the first and second twelve hour periods by group. A $p < 0.05$ was considered statistically significant.

Results: There were no catheter related problems. Respiratory depression was not noted in either groups. Results of pain scores and number of supplemental narcotic injection (TABLE 2) exhibited a strong trend in favor of the morphine/bupivacaine combination. Pruritis (A 3/10, B 6/10), nausea (A 1/10, B 2/10) and somnolence (A 4/10, B 6/10) were lower in the patients receiving fentanyl and bupivacaine.

TABLE 1: Pain Scores (mean ± S.D)

	PAR	4 hrs.	8 hrs.	12 hrs.	16 hrs.	20 hrs.	24 hrs.
Grp.	1.3±	4.1±	3.4±	3.4±	3.1±	3.2±	3.7±
A	.9	2.8	2.6	1.6	1.9	1.9	1.7
Grp.	4.1±	3.2±	2.4±	1.9±	1.8±	2.2±	1.3±
B	3.1	3.5	2.2	2.2	1.8	1.9	1.7

TABLE 2: Supplemental Narcotic Injection Doses Per Patient

	0-12 hrs.	12-24 hrs.
Group A	1	.25
Group B	.5	0

Discussion: The results of this study suggest greater analgesic effect and more side effects from the combination of morphine/bupivacaine as compared to fentanyl/bupivacaine. These findings may be due to the more rapid redistribution of the more highly liphophylic compound fentanyl compared to morphine. Other possibilities include the role of the side effects in overall preception of pain relief and the potential difference in potency and synergy of the drug combination when this route of administration is employed.

References:
1. Bahar M, Olshwang D, Magora F, Davidson JT: Epidural morphine in the treatment of pain. Lancet 1979;1:527-529.
2. Logas WG, Faber LP, El-Ganzouri A, Ivankovich AD: A prospective double-blind study for continuous thoracic epidural analgesia for thoracotomy patients. Anesthesiology 1984;61(3A):222.
3. Youngstrom P, Eastwood D, Patel H, Bhatia R, Cowan R, Sutheimer C: Epidural fentanyl and bupivacaine in labor: Double-blind study. Anesthesiology 1984;61(3A):414.
4. Skerman JH, Thompson BA, Goldstein MT, Jacobs MA, Gupta A, Blass NH: Combined Continuous epidural fentanyl and bupivacaine in labor: A randomized study. Anesthesiology 1985;63(3A):450.

TITLE: FRESH FROZEN PLASMA: JUSTIFICATION OF PERIOPERATIVE USE

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Introduction. A large proportion of Fresh Frozen Plasma (FFP) transfused in this country is used in the perioperative period. For this reason anesthesiologists are often involved in its administration. Because of recent concern that FFP is being inappropriately overutilized (1), we elected to examine the reasoning involved in decisions to transfuse FFP.

Methods. All patients receiving perioperative transfusions of FFP, at Temple University Hospital, between December, 1985 and March, 1986 (n=32) were identified by the blood bank. The total number of operative cases during that time period was 2077. The charts and anesthesia records were reviewed by the authors, within 48 h of surgery. Information sought included type of surgical procedure, estimated blood loss, blood products given, administration of antibiotics, warfarin or vitamin K, and pertinent laboratory studies (Hgb. Prothrombin Time (PT), PTT, Platelet count, creatinine, bili, AST, ALT, Alk Phos). The authors also interviewed the staff and resident anesthesiologist regarding justification for using FFP. A questionaire classified their response into 1 of 6 categories. Untoward bleeding was based on the staff anesthesiologist's assessment of the situation. Documentation of coagulopathy was based on the preoperative coagulation profile.

Table 1

Justification for use of FFP	Authors Assessment
1. Surgeon insists - no untoward bleeding	NI
2. Hypovolemia	NI
3. Presumed* coagulopathy-no untoward bleeding	NI
4. Presumed* coagulopathy & untoward bleeding	PI
5. Documented coagulopathy-no untoward bleeding	PI
6. Documented coagulopathy & untoward bleeding	I

*Presumption by the anesthesiologist

A definite indication (I) for transfusion of FFP was documented coagulopathy with untoward bleeding. Possible indications (PI) were defined as presumed coagulopathy with untoward bleeding, and documented coagulopathy without untoward bleeding. A designation of not indicated (NI) was assigned to hypovolemia, surgeon insistence or a presumed coagulopathy in the absence of untoward bleeding. Also, the combination of FFP with packed RBC during massive transfusion (replacement of $\geq$ 1 blood volume) in lieu of whole blood (WB) was considered inappropriate.

Results. Nineteen patients had cardiac surgery, 7 general surgery, 1 gynecologic, 1 urologic, 2 head and neck, and 2 had plastic surgery. Three patients had pre-existing liver disease. None had renal disease. Perioperative antibiotic therapy was of short duration and did not involve drugs known to affect coagulation. Seven patients had been taking warfarin chronically. All preoperative PT results were normal, with the exception of those obtained from patients on warfarin and two patients with liver disease. One patient required massive transfusion. Of the 7 patients receiving warfarin only 1 patient was given vitamin K preoperatively.

Forty seven percent of the patients received FFP for what we considered a definite or possible indication. Fifty three percent received FFP based on indications we considered inappropriate. The mean number of units of FFP/pt and post-op PT, are presented in Table 2 in relation to justification. In the 17 patients for whom transfusion of FFP was NI the preoperative PT was normal and the postoperative PT was < 15 seconds.

Table 2

Justification	Number of Patients	MEAN FFP Units/Pt.	MEAN (± SD) Post-op PT
1 (NI)	10	2.1	12.7 ± 1.52
2 (NI)	2	4.0	14.4 ± 0.14
3 (NI)	5	2.2	13.1 ± 0.87
4 (PI)	6	4.6	13.8 ± 1.68
5 (PI)	2	3.5	19.5 ± 5.23
6 (I)	7	6.0	15.4 ± 2.74

Discussion. Transfusion of FFP has increased tenfold, from 1974 through 1983, despite a paucity of indications for its use. (2) Our data indicate that the reasons given to justify its use are often inappropriate. It is interesting to note that the majority of patients in whom FFP was NI received 2 units, an amount considered by most to be inadequate for correction of coagulopathies due to factor deficiency or dilution. It seems unlikely that any benefit was accrued from this therapy.

When an acceptable alternative exists, such as vitamin K administration, consideration should be given to the therapy with least potential for harm. In our one case of massive transfusion, the use of WB, rather than FFP and packed RBC, would have accomplished the same objective at a lesser cost and risk to the patient.

It appears there is a need for re-education of both anesthesiologists and surgeons regarding indications for and actions of FFP. Transfusion of FFP is a costly, and potentially harmful, limited resource that should be used only when clearly indicated.

References.

1. Love JR. Fresh Frozen Plasma: Too Few Indication-Too Much Use. Anesth Analg 64:849-850, 1985

2. Fresh Frozen Plasma: Indications and Risks. National Institute of Health Consensus Development Conference Statement. Vol. 5, No. 5, 1984

Title: EFFECTS OF ISOFLURANE ON SINGLE ACETYLCHOLINE RECEPTOR CHANNEL KINETICS

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Introduction: The recent introduction of high-resolution ("gigaseal") patch-clamp techniques (1) has permitted direct observation of the molecular transitions of individual ion channels between open and closed (or blocked) states. In the presence of charged local anesthetics, the open state of the acetylcholine receptor channel is interrupted by numerous brief closures (2), thought to reflect intermittent blockade by anesthetic molecules. A similar "flickery" pattern is observed in the presence of uncharged local anesthetics (3) and barbiturates (4), although the interpretation of these findings is controversial. Here we report that the general anesthetic isoflurane also causes "flickering" of the acetylcholine receptor channel, and shortens the apparent mean duration of the open state.

Methods: BC3H-1 cells, which express acetylcholine receptor channels similar to those of the mammalian neuromuscular junction, were cultured and prepared for electrophysiological recording using methods described by Sine and Steinbach (5). Standard protocols (1) were followed to obtain on-cell membrane patches, using micropipettes containing 140 mM KCl, 5 mM MgCl2, 10 mM HEPES, 5 mM EGTA and either 0 or 600 micromolar isoflurane. Seal resistances were typically in the 30-100 gigaohm range. Single channel currents were amplified using a List EPC-7 I-V converter headstage and amplifier, recorded on FM magnetic tape, filtered at 1 kHz and digitized at 50 or 333 microseconds per point. The experiments were performed at room temperature.

Results: Examples of single channel currents activated by acetylcholine (0.5 micromolar) in the absence of isoflurane are shown in figure 1 (top panel). Brief closures are infrequent. By contrast when isoflurane is present in the micropipette (bottom panel), acetylcholine-activated single channel currents take the form of short bursts of openings, qualitatively exhibiting the "flickering" characteristic which has been observed in the presence of local anesthetics and barbiturates.

The superimposed histograms shown in figure 2 illustrate the shortening of burst durations by isoflurane. The closed bins represent the distribution of burst durations in the absence of isoflurane (192 events; mean duration 4.2 ms). The open bins show the distribution in the presence of 600 micromolar isoflurane (194 events; mean duration 2.2 ms).

Discussion: The appearance of "flickering" in the kinetic behavior of ion channels exposed to uncharged local and barbiturate anesthetics has been interpreted, in different contexts, as evidence favoring either a channel-blocking mechanism (2) or an allosteric modification of rate constants governing transitions between the open state and one or more normally occult closed states (3). Our experiments establish that a general anesthetic (isoflurane) causes the acetylcholine receptor channel to "flicker," but they do not discriminate among several proposed physical mechanisms. It seems unlikely, however, that a simple channel-blocking mechanism (cf. Neher and Steinbach, 1978) can fully explain the present results, as it predicts a concentration-dependent lengthening rather than a shortening of the burst duration. Detailed quantitative studies of these phenomena are now required.

References:

1. Hamill OP, Marty A, Neher E, Sakmann B and Sigworth FJ. Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches. Pflugers Arch. 1981; 391:85.
2. Neher E and Steinbach JH. Local anesthetics transiently block currents through single acetylcholine receptor channels. J. Physiol. 1978; 277:153.
3. Ogden DC, Siegelbaum SA and Colquhoun D. Block of acetylcholine-activated ion channels by an uncharged local anesthetic. Nature 1981; 289:596.
4. Gage PW and McKinnon D. Effects of pentobarbitone on acetylcholine-activated channels in mammalian muscle. Br. J. Pharmacol. 1985; 85:229.
5. Sine SM and Steinbach JH. Activation of a nicotinic acetylcholine receptor. Biophys. J. 1984; 45:175.

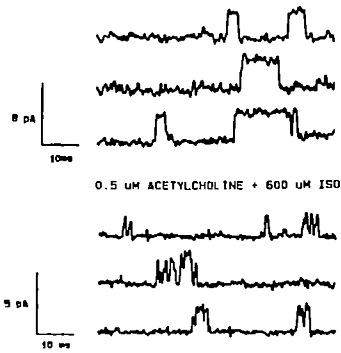

Figure 1
Single channel currents +/- 600 micromolar isoflurane

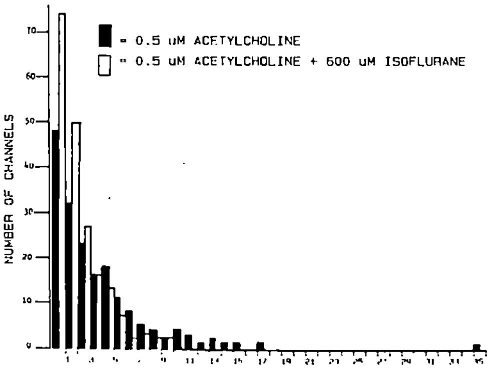

Figure 2
Burst durations +/- 600 micromolar isoflurane

Title: ISOFLURANE BLUNTS THE NOREPINEPHRINE RESPONSE TO CARDIOPULMONARY BYPASS

Authors: Paolo Flezzani, M.D., Narda Croughwell, C.R.N.A., R. William McIntyre, M.D. and J.G. Reves M.D.

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Introduction. Cardiopulmonary bypass (CPB) elicits a complex neurohumoral response, consisting primarily of increases in norepinephrine and epinephrine. In a previous study, epinephrine was reported to increase six fold, while the norepinephrine increase was two-fold. However, only norepinephrine levels correlated with changes in hemodynamics (1). We tested the hypothesis that anesthetic depth blocks the catecholamine response to CPB. We used an inhalation agent since these anesthetics can be given at a constant inspired concentration and have been proven effective in blunting the hormonal response to CPB without significant side-effects (2). Isoflurane was selected because of its vasodilating effect.

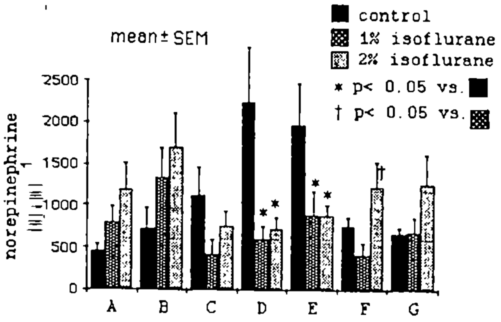
Methods. Eighteen patients scheduled for elective coronary revascularization gave informed consent. General anesthesia was induced with fentanyl (30 mcg.kg^{-1}) and oxygen and maintained with a continuous infusion of fentanyl (0.2 mcg.kg^{-1}.min^{-1}). The fentanyl infusion was terminated just before the beginning of CPB. Six patients were randomly assigned no further anesthetic during CPB. The other twelve received a continuous inspired concentration of isoflurane, either 1% or 2%, from the beginning of CPB until five minutes after the removal of the aortic cross-clamp. During CPB, pump flow was kept constant at 1.6 l.min^{-1}.m^{-2}, mean arterial pressure at 50±10 mmHg, and temperature at 27°C. At seven times during the procedure, blood samples were withdrawn for determination of plasma epinephrine and norepinephrine by HPLC. Plasma CK-MB was measured 10 hours after the end of CPB.

Statistical analysis was performed using paired t-tests within groups and analysis of variance and paired t-tests were used between groups. Significance was declared when $p<0.05$ and results are presented as mean ± SEM.

Results. Groups had similar age, body surface area, ejection fraction and coronary anatomy. Norepinephrine levels are shown in the figure. There was a significant decrease in norepinephrine in the period following the removal of the aortic cross-clamp in the isoflurane groups. This effect lasted until weaning from CPB, when plasma levels returned to baseline and was not related to isoflurane dose. There was a trend for epinephrine to be lower in the isoflurane groups, but this did not attain statistical significance. There was no difference between groups with regard to total dose of fentanyl, aortic cross-clamp time and duration of CPB. Directly measured and derived hemodynamics were not different during and after CPB. However, during CPB, the maximal infusion rate and the total dose of SNP infused were higher in the control group than in the isoflurane groups. Total amount of phenylephrine infused was highest in the 2% isoflurane group. CK-MB was normal in all groups.

Discussion. Catecholamine release reflects the adrenocortical response to the stress of CPB. Our data confirm previous reports, that the delivery of anesthesia during CPB blunts, but does not abolish, the stress response to CPB. We have demonstrated that the effect of isoflurane on the norepinephrine rise during CPB is not dose related; however, there was a dose related difference in norepinephrine level after CPB (Fig.1, F). In addition, our results suggest an effect of isoflurane on epinephrine during CPB. These effects are diminished immediately after the conclusion of CPB, when plasma catecholamine levels return towards baseline. In conclusion, isoflurane can decrease the circulating catecholamine level during the myocardial reperfusion following the removal of aortic cross-clamp. Further investigation is needed to determine whether this effect contributes to the recovery of myocardial function.

Figure 1



Where A=after sternotomy, B=on CPB, C=30 min cross-clamped, D=2 min cross-clamp off, E=10 min cross-clamp off, F=off CPB, G=chest closed

References.

1. Reves JG, Karp RB, Buttner EE et al. Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man. Circulation 1982;66:49-55.
2. Samuelson PN, Reves JG, Kirklin JK, Bradley E, Wilson KD, Adams M. Comparison of sufentanil and enflurane-nitrous oxide anesthesia for myocardial revascularization. Anesth Analg 1986;65:217-26.

Title: THE BENZODIAZEPINE ANTAGONIST RO 15-1788 REVERSES MIDAZOLAM-INDUCED EEG-CHANGES POSTOPERATIVELY

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Introduction. EEG-changes seem to reflect the level of vigilance in patients in the intra-as well as the post-anesthetic period. Thus, the dynamic effects of centrally active compounds can be monitored. Little is known about the dynamic, cortical effects of the new benzodiazepine midazolam, which due to its shorter duration of action and superior amnestic effect in comparison to other benzodiazepines, seems to be a suitable induction agent for anesthesia. The alleged short duration, however, has not been sufficiently demonstrated under clinical circumstances. In order to demask any long-term cerebral effects, the specific antagonist **Ro 15-1788**, given at the end of anesthesia, is a tool to demonstrate any possible overhang which concomitantly will result in a change of EEG-activity.

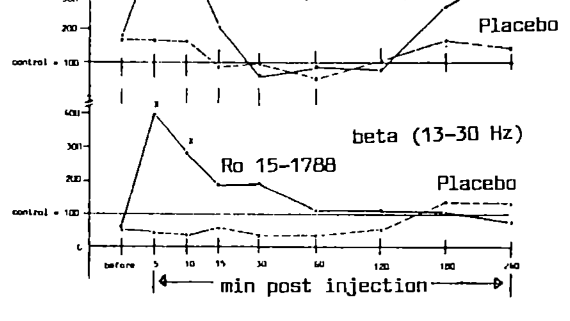
Methods. 20 patients after institutional approval and informed consent, who underwent elective abdominal, upper or lower extremity surgery, received midazolam as the induction agent after premedication (atropine 0.01 mg/kg, meperidine 1 mg/kg, promethazine 0.5 mg/kg). The benzodiazepine was given in titrated doses over 20 to 30 seconds until the desired effect was obtained, followed by succinylcholine, intubation and mechanical ventilation under ethrane N_2O/O_2-relaxant (vecuronium) anesthesia. 10 patients received Ro **15-1788** (0.8 mg/70 kg) while another group of 10 patients received placebo in a double-blind fashion at the end of operation. For the evaluation of vigilance the EEG was recorded from position Fp1-A1 prior to induction, and then for the following 240 postoperative minutes. The EEG-signal was fed on-line into a **Lifescan**™ cerebral monitor (Neurometrics, San Diego, California) which performed an aperiodic analysis every 2 seconds. Data were collected at 5-10-15-30-60-120-180 and 240 minutes after drug administration over a time intervall of 1 minute. The cumulative power (μV^2) in the classical frequency bands (delta, theta, alpha, beta) was computed via an integrated PC (Kaypro™ 2000), using a specifically designed software program to quantify data acquisition and analysis of preprocessed EEG-signals in real time.

Results. In regard to mean age, amount of midazolam given for induction, and duration of anesthesia, both groups of patients (Ro 15-1788 and placebo) showed no significant differences (mean age 33 and 36 respectively; mean duration of operation 119 and 124 minutes respectively; mean total dose of midazolam in both groups 13.3 mg).
The Ro 15-1788 group showed a significant faster recovery which was reflected in the EEG-power spectra. In the Ro 15-1788 group there was an almost immediate (5 min) increase in beta-activity of 350 % when compared to the premedicated, awake state, and 300 % when compared to placebo. This increase in vigilance coincided with a concomitant reduction of power in the theta-band, showing a significant difference between both groups of 1790 %. Both effects subsided over the next 30 min, suggesting a short duration of action of the antagonist (fig.).
However, in addition to the increase in vigilance, delta-activity in the Ro 15-1788 group showed marked fluctuation with sinus wave-like changes over 1 min recordings. Thus, the power in the delta-band was also higher when Ro 15-1788 had been administered (fig.).

Discussion. The power-changes in the various EEG-frequency bands demonstrate that midazolam, even after a mean operation time of 123 minutes, still exhibits a significant effect on cortical activity in the postoperative period, resulting in reduced vigilance. This correlates with the elimination half-life (t 1/2B) which has a duration of 1.5-2.5 hours (1), suggesting that even after two hours, depressive central effects may still be present. The antagonistic activity, i.e the increase in vigilance, is markedly reflected in the beta-band, the fast frequency domain of the EEG. In a study by other researchers (2,3) using the EEG as a tool to evaluate postoperative vigilance changes after sufentanil and fentanyl-droperidol anesthesia, beta-activity was considered as the parameter reflecting recovery from anesthesia.
But in addition to its antagonistic effect, Ro 15-1788 also seems to inherit some agonistic, non-benzodiazepine properties. This was reflected in a significant increase in μV^2 in the delta-band of the Ro 15-1788 group. The oberservation is underlined by studies where the sole administration of the antagonist increased delta-activity in the normal sleep-waking cycle of dogs (4). Such observations could also be derived from the present study, where patients after Ro 15-1788 seemed asleep however, were wide awake when adressed.

References.

1. Amrein R, Cano JP, Eckert M, Coassolo P. Pharmakokinetik von Midazolam nach intravenöser Gabe. Arzneimittelforsch 1981; 31(II):2202.
2. Bovill JG, Sebel PS, Wauquier A, Rog P. Electroencephalographic effects of sufentanil anaesthesia in man. Br J Anaesth 1982; 54:45.
3. Freye E, Hartung E, Buhl R. Alfentanil als letzte Dosis (on-top) in der Neuroleptanalgesie mit Fentanyl. Anaesthesist 1986; 35:231.
4. Wauquier A, Ashton D. The benzodiazepine antagonist Ro 15-1788 increases REM and slow wave sleep in the dog. Brain Res 1984; 308:159.



Title: REPRODUCTIVE AND TERATOGENIC EFFECTS OF NITROUS OXIDE, FENTANYL AND THEIR COMBINATIONS IN SPRAGUE-DAWLEY RATS

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Introduction: Administration of 75% nitrous oxide (N_2O) to Sprague-Dawley rats for 24 hours on day 9 of pregnancy results in increased fetal loss and teratogenic effects. However, the minimum toxic concentration of N_2O administered for 24 hours on day 9 is not known, although, in a previous study we showed that 25% N_2O was devoid of adverse effects.[1] Also, it is not known if administration of other CNS depressant drug in combination with N_2O, as is done in clinical anesthesia practice, would increase its reproductive toxicity. The present study was designed to answer these questions.

Methods: 429 timed pregnant Sprague-Dawley rats were obtained from the breeder on day 6 of pregnancy, weighed and assigned to six groups of approximately equal average weight as follows: 1) Control (n=114); 2) Fentanyl (n=60); 3) 35% N_2O (n=54); 4) 35% N_2O + Fent (n=73); 5) 50% N_2O (n=54); 6) 50% N_2O + Fent (n=74). On day 7 of pregnancy, osmotic minipumps (Alza Corp, Palo Alto, CA) which deliver their contents continuously and at a constant rate for two weeks were implanted subcutaneously in the back of the rats. The total daily fentanyl dose was 500/ug/kg/day; rats in control and N_2O alone groups received normal saline. On day 9 of pregnancy, rats were administered N_2O for 24 hours; control and fentanyl only groups were exposed to room air simultaneously in another chamber. On day 21 of pregnancy, rats were killed, cesarean sections were performed, and the uterine contents were examined. Each fetus was examined for external abnormalities and its weight and sex determined. Fetuses then were fixed and stained, and examined microscopically either for visceral or skeletal abnormalities. Statistical comparison were made with ANOVA, chi square or t tests, as appropriate. $p < 0.05$ was considered statistically significant.

Results: One rat in the fentanyl group, 10 rats in the 35% N_2O + Fent group and 41 rats in the 50% N_2O + Fent group died during exposure. Total weight gain during the experiment was less than control only in rats from the 50% N_2O and 50% N_2O + Fent groups. There were no differences in the overall pregnancy rate and in the total number of implantations among all the groups. However, the total number of live fetuses per dam was less, and the total number of resorptions per dam and the post-implantation fetal loss were more in 50% N_2O and 50% N_2O + Fent groups than in the control group. A total of 2693 offspring were delivered. There were no differences in external abnormalities in any of the groups. The incidence of major and minor visceral abnormalities were increased in 50% N_2O and 50% N_2O + Fent rats and there also was an increase in minor skeletal anomalies in these rats. Skeletal developmental variants were increased in 35% N_2O + Fent and 50% N_2O + Fent groups (combined treatment) but not in the corresponding N_2O alone groups.

Discussion: The present study defines the minimum toxic concentration of N_2O administered for 24 hours on day 9 of pregnancy: 35% N_2O is not associated with adverse reproductive effects but 50% N_2O is toxic. Given this information we then were able to determine if the combination of N_2O and another CNS depressant drug, fentanyl, altered the threshold of reproductive toxicity of N_2O. In a previous study employing osmotic pumps, we administered fentanyl doses as high as 500 ug/kg/day on days 3-17 and neither adverse reproductive nor teratogenic effects were observed.[2] In the present study, N_2O exposure on day 9 of pregnancy was accompanied by significant maternal toxicity in the combined treatment groups, as evidenced by an intra-anesthetic mortality rate of 14% for the 35% N_2O + Fent group and 55% for the 50% N_2O + Fent group. There were no intra-anesthetic deaths in the N_2O alone treated dams. Thus, the 50% N_2O + Fent treatment was at the upper limit of maternal tolerance. In spite of this, there was only one clear-cut reproductive effect which occurred in the combined treatment groups but not in either group treated with N_2O alone; i.e., an increased incidence of skeletal developmental variants. Developmental variants are abnormalities in anatomic structure which, themselves, have no significant biological effect. Some, such as extra 14th rib, are indicative of teratogenic potential.[3] These were not seen in the present study. Thus, we conclude that the addition of fentanyl to N_2O does not increase the toxic reproductive or teratogenic effects of N_2O.

References:
1. Mazze et al. Teratology 30:259-265, 1984
2. Fujinaga et al. Teratology (In Press)
3. Kimmel and Wilson. Teratology 8:309-315, 1973

Summary of Reproductive Indices and Fetal Exam.	Cont	Fent	35% N2O	35% N2O+ Fent	50% N2O	50% N2O+ Fent
No. of rats studied	114	60	54	73	54	74
No. of rats died during exposure	0	1	0	10	0	41
Starting dam weight (g)	213	213	212	212	212	212
Weight loss during exposure (g)	23	27*	24	30*	29*	32*
Weight gain during pregnancy (g)	135	129	139	127	106*	96*
Overall pregnancy rate (%)	75	78	76	64	76	66
Total implantations/dam	11.8	11.5	12.3	12.6	11.7	10.7
Total live fetuses/dam	11.2	10.9	11.6	10.9	7.7*	6.4*
Total resorptions/dam	0.5	0.6	0.6	1.2	4.1*	3.9*
Post-implantation loss (%)	5.8	5.8	5.4	13.4	34.0*	43.0*
Mean fetal weight (g)	4.5	4.5	4.5	4.3	3.9	3.9
Fetal females (%)/dam	51	47	49	52	52	54
No. of fetuses examined:						
External examination	954	510	479	342	306	102
Visceral examination	474	256	241	171	153	51
Skeletal examination	480	254	238	153	171	51
External examinations:						
Major malformations/liter (%)	0.0	0.1	0.4	1.2	0.8	1.1
Minor anomalies/liter (%)	0.3	0.4	0.4	1.2	0.6	1.1
Runts/liter (%)	0.6	0.2	0.7	0.9	1.3	1.1
Visceral examinations:						
Major malformations/liter (%)	0.0	0.0	0.3	0.7	6.1*	15.7*
Minor anomalies/liter (%)	4.7	4.6	6.3	8.5	17.8*	20.9*
Devel. variants/liter (%)	1.2	0.0	0.0	0.0	0.0	0.0
Skeletal examinations:						
Major malformations/liter (%)	0.0	0.0	0.4	1.7	1.1	0.0
Minor anomalies/liter (%)	0.6	2.2	0.8	1.1	7.6*	9.5*
Devel. variants/liter (%)	29.0	21.1	41.9	58.2*	35.8	68.3*

* $p < 0.05$ (compared with control)

Title: SUFENTANIL PHARMACOKINETICS IN PATIENTS UNDERGOING RENAL TRANSPLANTATION

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Introduction: Renal transplantation has become a common surgical procedure. Because of physiologic changes associated with chronic renal failure, chronic dialysis and the underlying disease, these patients frequently have disturbances in distribution of intravascular and extravascular volume and secondary alterations in drug distribution. This study was designed to determine the pharmacokinetics of sufentanil in patients undergoing renal transplantation.

Methods: The patient population consisted of 10 patients (ages 28-47) with chronic renal failure, on chronic hemodialysis who underwent renal transplantation. None of the patients has a history of liver disease. General anesthesia was induced with thiopental 5-7 mg/kg IV and endotracheal intubation was facilitated by atracurium .4 mg/kg IV. Anesthesia was maintained with isoflurane .5-1% (inspired concentration) as needed and nitrous oxide: oxygen 50:50. Sufentanil 2 mcg/kg was administered as an intravenous bolus in a peripheral vein. Blood samples for sufentanil assay were obtained from a central venous line at 1,3,5,7,10,15,20,30 and 60 minutes and every hour for six hours after drug administration and at extubation. Time from sufentanil administration until the point at which patients were adequately ventilating sponteneously was also recorded. Plasma samples were separated and frozen until radioimmunoassay was done, (sensitivity .1 ng/ml). Plasma concentration decay curves were fitted for each patient to bi-and triexponential equations. This was done using weighted, nonlinear least squares regression analysis. Derivation of pharmacokinetic parameters were in accordance with formulas described in Gibaldi (1).

Results: Seven patients received kidneys from living, related donors and three underwent cadaveric transplants. Although both bi- and triexponential equations described plasma decay curves well, the biexponential equation provided the best fit (2).

Pharmacokinetic data are presented in table 1. Values for the parameters measured are as follows (mean ± SEM): Volume of central compartment, .15±.05 l/kg; volume of distribution, .85±.16 l/kg; elimination half-life, 176±87 min. and clearance; 11.5±4 ml/kg/min. Most patients experienced a transient increase in plasma sufentanil levels between 180-240 minutes after injection; 60-120 minutes after the transplanted kidney was revascularized. Only one patient experienced prolonged respiratory depression and most other patients were extubated within forty minutes following completion of surgery. The average duration of respiratory depression after sufentanil administration was 235±113 mins. and the average length of surgery was 165±32 mins.

Discussion: The pharmocokinetic parameters of sufentanil are nearly identical in renal transplant and healthy surgical patients (3). This suggests that liver function is well maintained and is the primary determinant of sufentanil clearance. This is suggested by the clearance value in the respective groups above; 11.5 and 12.7 l/kg/min. It also implies that renal function plays little if any role in the elimination of sufentanil during the first few hours after administration. The only parameter that differed was the volume of distribution .85 l/kg in the transplant patients as compared to 2.86 l/kg in a normal population (3). These differences may be attributed to volume alterations following presurgical hemodialysis. In fact eight out of ten patients had been dailyzed within 12 hours prior to surgery. Another potential cause for this discrepancy is sampling from the right atrium versus superior vena cava. Finally, the mathematical derivation of the volume of distribution values were sensitive to the transient post-revascularization increases in plasma drug concentrations in the transplant patients. The overall contribution of this phenomenon was not determined in this study. Volume loading with 3-4 liters of crystalloid fluid after the renal anastomases were complete appeared to have little effect on the drug's pharmacokinetics. This finding is most likely related to the timing of fluid administration approximately 90 minutes after sufentanil administration when redistribution of the drug had already occured. In conclusion, sufentanil pharmacokinetics are essentially the same in patients undergoing renal transplantation, compared to patients with normal renal function. Furthermore, these patients did not exhibit a clinically significant increase in sufentanil-induced respiratory depression, as demonstrated by adequate spontaneous ventilation at either the termination of surgery or shortly afterwards.

References:

1. Gibaldi M, Perrier D. Pharmacokinetics 2nd Ed. Marcel Dekkam, Inc. New York, N.Y. 1982

2. Boxenbaum HG, Riegelman S, Elashoff RM. J Pharmacokin Biopharm 2:123-148, 1974.

3. Bovill JG, Sebel PS, Blackburn CL, et al Anesthesiology 61:502-506, 1984.

Table 1: Pharmacokinetic parameters (mean ± SEM)

VC (l/kg^{-1})	V Beta ($l:kg^{-1}$)	+½B (min.)	CL ($ml/kg:min^{-1}$)
.15±.05	.85±.16	176±87	11.5±3.7

Title: COMPARATIVE STUDY OF LABETALOL AND HYDRALAZINE IN THE TREATMENT OF POSTOPERATIVE HYPERTENSION

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Introduction: Hypertension is a common occurrence in the immediate postoperative period and may lead to serious complications. Vasodilators such as hydralazine (H) used to treat postoperative hypertension (PH) produce a hyperdynamic state which may lead to potentially deleterious effects in patients with coronary artery disease. Labetalol (L) is a nonselective beta blocker with significant alpha blocking properties that reduces the systemic vascular resistance without producing a reflex tachycardia. This property of L offers potential advantages in the treatment of hypertension. The purpose of this study was to determine efficacy of L in comparison to H in the management of PH.

Methods: Twenty patients (average age 68 ± 4 yrs; average weight 59 ± 3 kg) with a history of hypertension and undergoing major surgery were studied during the postoperative period. Institutionally approved informed consent was obtained during the preoperative visit. Patients were randomized and treated for PH with either IV L (group L, 10 patients) or IV H (group H, 10 patients). Treatment was initialized when systolic blood pressure (SBP) was over 180 mmHg and diastolic blood pressure (DBP) 100 mmHg. Treatment was aimed at achieving a 20% reduction of the systolic blood pressure and a diastolic blood pressure of 90 mmHg or less. Patients with contraindications to beta blockers were excluded from the study. Prior to initiation of antihypertensive therapy common causes of postoperative hypertension were eliminated such as pain, bladder distension, hypoxia, hypercapnia and hypervolemia. Blood pressure (SBP, DBP, MAP) was monitored by a Dinamap or direct arterial catheter every 5 minutes. The electrocardiograph (modified V5 chest lead) was continuously monitored for at least 2 hours. Patients in Group L were given an intravenous bolus of 10mg initially.
If needed this was increased to 20mg, then 40mg at 5 minute intervals. A maximum dose of 150mg of L was administered in 25 minutes. Patients in group H were given an intravenous bolus of 5mg initially, and if necessary followed by doses of 10mg and 15mg, at 10 minute intervals for a total of 30mg in 30 minutes. Blood pressure and heart rate at initiation of therapy (base line) were compared with values at 10, 30, 60, and 120 minute intervals in each group. Statistical data was analyzed by paired Students T-test, using p 0.05 as significant.

Results: There were no significant differences between groups L and H in the baseline HR, SBP, DBP, and MAP. Table 1 summarizes the hemodynamic effects of both drugs. L and H produced significant reduction in blood pressure (SBP, MAP, DBP) within 10 minutes, which lasted at least 2 hours. One patient in each group failed to respond. There was no precipitous fall in blood pressure in either group. L produced a significant reduction in the HR and RPP without producing bradycardia. Hydralazine did not produce a statistically significant increase in pulse rate due to the large variability around the mean values, but three patients developed sinus tachycardia and required IV propranolol, and two of these three patients developed transient ST segment depression.

Discussion: Intravenous labetalol administered in incremental fixed doses starting with 10 mg was a safe and effective agent in producing adequate reduction in blood pressure, heart rate and rate pressure product in the postoperative patients. This effect was maintained for at least 2 hours without an overshoot. H was equally effective in lowering BP, but produced a 30% incidence of increased HR. L significantly lowers HR as well as BP and therefore, may be useful in the treatment of PH in patients who would otherwise not tolerate tachycardia.

References:
1. Cummings AMM, Brown JJ, Lever AF, et al: Treatment of severe hypertension by repeated bolus injections of labetalol. Br. J. Clin. Pharm. 1979; 8:199S-204S.
2. Prichard BN: Labetalol, An alpha and beta adrenoceptor blocking agent: Its use in therapeutics. Br. J. Clin. Pharm. 1979; 8:239S-244S.

Table 1
COMPARISON OF IV LABETALOL VS HYDRALAZINE

			Time after Drug Injection (minutes)			
	Group	Baseline	10	30	60	120
Heart Rate BPM	L	89 ± 13.4	72 ± 7*	70 ± 8.1*	69 ± 5.1*	71 ± 9.1*
	H	74 ± 8.2	90 ± 17.5	82 ± 12.4	78 ± 12.5	79 ± 13.2
SBP mmHg	L	219 ± 20.7	164 ± 15.1*	164 ± 20.4*	140 ± 15.8*	156 ± 16*
	H	209 ± 20	169 ± 14.8*	160 ± 24 *	161 ± 15.2*	145 ± 20.1*
DBP mmHg	L	110 ± 23	82 ± 10.2*	82 ± 13*	78 ± 8.5*	73 ± 7.3*
	H	98 ± 18	79 ± 14.2*	70 ± 19*	68 ± 14.1*	63 ± 13.3*
MAP mmHg	L	149 ± 26	124 ± 16*	109 ± 13*	102 ± 13*	107 ± 12.1*
	H	136 ± 15.1	113 ± 13.4*	99 ± 15*	97 ± 13.2*	89 ± 4.6*
RPP†	L	19.8± 2.6**	12.1± 2.3*	11.5± 2.5*	11.1± 2.5*	11.2± 2.1*
	H	15.2± 3.2	12.0± 5	11.5± 2.8*	11.6± 2.9*	10.9± 2.9*

Mean values ± Standard Deviation
† No. x 10^3

*p<0.05 within group
**p<0.05 between groups

Title: EFFECTS OF HALOTHANE AND ISOFLURANE ON THE BARORECEPTOR RESPONSE IN NEWBORN SWINE

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Introduction: The baroreflex, an important mechanism to maintain cardiovascular homeostasis, is immature in the newborn and obtunded during halothane anesthesia.[1] The effect of isoflurane on this response in the newborn is unknown. Furthermore, it has been suggested that the baroreceptor response may differ following pressor and depressor challenges.[2] Therefore, we compared the effects of equipotent concentrations of halothane and isoflurane on the baroreceptor response in newborn swine and the relative depression of the pressor and depressor responses.

Methods: With approval from the Animal Care Committee, eight fasting, unpremedicated newborn swine, ages 4-10 days, weighing 1.5-3.0 kg were studied. Each swine was randomly assigned to receive either halothane or isoflurane and the anesthetic requirement determined for that swine. A central venous catheter and a carotid artery catheter were then inserted. After the swine was allowed to recover for forty-eight hours, the awake heart rate, systolic blood pressure, and the baroreceptor response were recorded. Baroreceptor responses to both pressor (phenylephrine 50 µg intravenously) and depressor challenges were administered (sodium nitroprusside infusion) in a random sequence. The subsequent changes in heart rate and systolic blood pressure were recorded on a Hewlett-Packard 8 channel recorder. Anesthesia was then induced with the assigned anesthetic agent, the trachea was intubated and the lungs were mechanically ventilated to maintain normocapnia (pCO_2 35-45 mm Hg). End-tidal anesthetic concentrations (0.5 MAC, 1.0 MAC and 1.5 MAC) were administered in a random sequence. The baroreceptor response to pressor and depressor challenges were repeated at each MAC multiple. The slope of the linear portion of the R-R interval (heart rate) versus systolic blood pressure was determined to compare the sensitivity of the baroreceptor responses. The data was analyzed using least squares linear regression analysis.[3] Baroreceptor slopes at each MAC multiple were compared to awake values using two-way ANOVA and the Student-Newman-Keuls test.

Results: The mean age and weight of the swine in the halothane and isoflurane groups did not differ significantly. The mean (± SD) awake values for the pressure and depressor baroreceptor responses did not differ significantly (Table). The baroreceptor response decreased significantly compared to awake values at 1.0 and 1.5 MAC for both anesthetics (Figure). However, the baroreceptor response did not differ significantly between halothane and isoflurane at equipotent concentrations.

Discussion: The results of this study indicate that both halothane and isoflurane depress the baroresponse in newborn swine at 1.0 and 1.5 MAC. However, there was no significant difference between the pressor and depressor responses at equipotent concentrations of both halothane and isoflurane.

This work was supported with grants from Connaught Laboratories and the Heart and Stroke Foundation of Ontario.

References:

1. Wear R, Robinson S, Gregory GA. The effect of halothane on the baroresponse of adult and baby rabbits. Anesthesiology 1982; 56:188-91
2. Goldstein DS, Horwitz D, Keiser HR. Comparison of techniques for measuring baroreflex sensitivity in man. Circulation 1982; 66:432-9
3. Smyth HS, Sleight P, Pickering GW. Reflex regulation of arterial pressure during sleep in man: a quantitative method of assessing baroreflex sensitivity. Circ Res 1969; 24:109-21

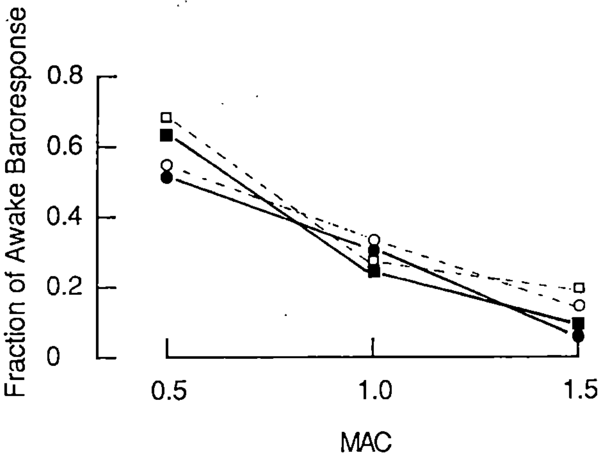
TABLE

AWAKE BARORECEPTOR SLOPES

	HALOTHANE	ISOFLURANE
Pressor	4.65 ± 1.20	4.89 ± 0.84
Depressor	4.50 ± 1.17	5.40 ± 1.09

Data (msec/mmHg) are mean ± S.D.

FIGURE



○ Halothane pressor response
● Halothane depressor response
□ Isoflurane pressor response
■ Isoflurane depressor response

TITLE: A COMPARISON IN PRIMATES OF THE TOLERANCE TO FOCAL CEREBRAL ISCHEMIA DURING ISOFLURANE OR NITROPRUSSIDE INDUCED HYPOTENSION

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Introduction: Both isoflurane and nitroprusside (SNP) are used to induce hypotension during neurovascular surgery. Isoflurane has properties that suggest that it may provide cerebral protection - $CMRO_2$ is markedly reduced while CBF is maintained and, in animal studies, survival during shock and hypoxia is prolonged.[1,2] However, a recent study in which vasopressors were used to maintain a normal BP did not demonstrate any benefit of high dose isoflurane in focal cerebral ischemia.[3] In this study, we have evaluated the cerebral protective effects of isoflurane during induced hypotension in a primate model of focal cerebral ischemia.

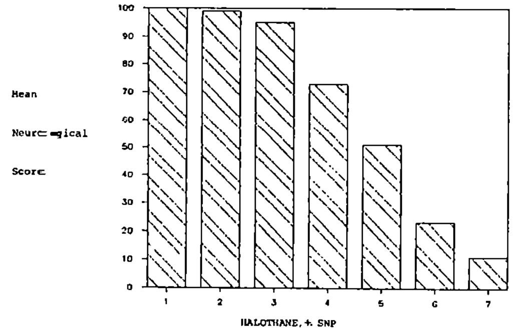
Method: Fourteen healthy female macaque monkeys were studied. The anesthesia sequence was ketamine (10 mg/kg), intubation, paralysis (gallamine) and ventilation (O_2/air, FIO_2 0.6) to $PaCO_2$ 35 mmHg. The animals were then divided into 2 groups. Seven animals received halothane and seven isoflurane anesthesia. During surgical preparation the halothane or isoflurane were titrated to keep BP in the normal range. Monitoring included intra-arterial pressure, arterial blood gases, EEG, somatosensory evoked potentials (SSEP), and temperature.

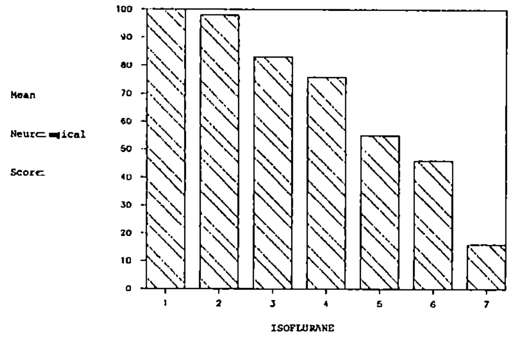
After transorbital exposure of the middle cerebral artery (MCA), in the halothane group, the inspired halothane was reduced to 0.75% and the mean BP reduced to 45 mmHg by the infusion of SNP. In the isoflurane group, the isoflurane was titrated to reduce mean BP to 45. Stable hypotension was maintained for 22.5 minutes and then the MCA occluded for 45 minutes. After deocclusion, hypotension was maintained for a further 22.5 mintues ie. 90 minutes hypotension in total. When normotension was re-established, the wounds were closed and the animals allowed to awaken. The animals were neurologically assessed every eight hours using a previously described scoring system (100 = normal).[4] On the third postoperative day, they were re-anesthetized and underwent NMR imaging, and EEG and SSEP recording. Thereafter they were sacrificed and the brains fixed for neuropathology.

Results: There were no differences between the groups in BP, PCO_2, temperature, and duration of hypotension and occlusion. Hypotension was more easily achieved and controlled with isoflurane. Normothermia was maintained in all. In every animal, SSEP disappeared within 10 minutes of MCA occlusion and recovered partially or completely on deocclusion. All awoke at the termination of the surgical procedure but 2 halothane and 0 isoflurane animals died prematurely ($p<0.2$). There were no statistically significant differences in neurological scores or in the NMR assessment of lesion sizes between the groups.

Discussion: These results indicate that isoflurane induced hypotension does not protect the brain during temporary focal ischemia when compared to SNP. The reason for such failure is unclear but suggests that isoflurane may not further depress metabolism in a focal ischemic region or that the cerebral vasodilatory effects of isoflurane may offset any metabolic benefit (steal phenomenon). In conclusion, while isoflurane produced more easily controllable hypotension, it offers no cerebral protective advantage over SNP in this model of focal cerebral ischemia.

References:
1. Newman B, Gelb AW, Lam AM. The effect of isoflurane-induced hypotension on cerebral blood flow and cerebral metabolic rate for oxygen in humans. Anesthesiology 19[illegible];64:307-310.
2. Newberg L, Milde J, Michenfelder J. Cerebral protection by isoflurane during hypoxemia or ischemia. Anesthesiology 1984;59:23.
3. Todd MM, Hehls DG, Drummond JC, Spetzler RF, Thompson R, Johnson P. A comparison of the protective effects of isoflurane and thiopental in a primate model of temporary focal cerebral ischemia. Anesthesiology 19[illegible];63:A412.
4. Spetzler RF, Selman WR, Weinstein P, Townsend J, Mehdorn M, Telles D, Crumrine RC, Macko R. Chronic reversible cerebral ishemia: evaluation of a new baboon model. Neurosurg 19[illegible];7:257-261.





TITLE: THE EFFICACY OF INHALATION ANESTHESIA VS INTRAVENOUS ANESTHESIA USING A COMPUTER ASSISTED INFUSION DEVICE.

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INTRODUCTION: Maintenance of anesthesia using primarily an intravenous agent in noncardiac surgery is a relatively new technique. Past studies have attempted to quantify the physiological differences between anesthesia maintained with an inhalation versus an intravenous drug. These studies however, have suffered from the inability to administer these two different forms of anesthesia by the same method. This is because there has previously been no administration system that enabled the plasma level of the intravenous anesthetic (that concentration which is in equilibrium with the CNS) to be maintained or altered accurately by the physician as can be done using a vaporizer. Also a value such as M.A.C for an intravenous drug, which provides the clinician with a dose guide for an adequate depth of anesthesia has not previously been known. These obstacles in performing a comparison have been overcome in this study by a) the use of computer assisted continuous infusion (CACI) which like a vaporizer for inhalational anesthesia provides a set plasma level of the intravenous drug and b) the knowledge of the MIC (minumum intravenous concentrations = Cp50) values for alfentanil, which provides a value equivalent to M.A.C^2. This study therefore for the first time compared the maintenance of anesthesia, hemodynamic stability and the recovery from anesthesia between halothane (H), fentanyl (F) and alfentanil (A) when all anesthetics were administered continuously at or around their MAC or MIC.

METHODS: This study was approved by the Institutional Review Board and patients gave written informed consent. Thirty patients scheduled for elective surgery were enrolled in the study and randomly assigned to one of the three groups (Group H, F, and A) cosisting of 10 patients per group. Premedication consisted of valium 10 mg P.O. one hour prior to surgery. Blood pressure and heart rate were recorded following specific stimuli and at 5 mins intervals. Following preoxygenation the patient was induced with thiopental 3-7 mg/kg, nitrous oxide 60 to 70% in oxygen was added and vecuronium 0.1 mg/kg was given. After induction, Group H patients received halothane as the basic anesthetic for the remainder of the procedure. Group F and A patients received fentanyl and alfentanil respectively for the remainder of the procedure. The plasma concentration of all agents was varied as needed to maintain an adequate depth of anesthesia, and the heart rate and blood pressure within 20% of baseline values. For all 3 groups anesthesia was used in a physician closed loop mode with the physician (anesthesiologist) changing the set point, thus moving the plasma concentration from one plateau to the next either by vaporizor (H) or CACI (A,F). End tidal, halothane was measured using a Puritan Benet Agent Monitor. Time from the end of the procedure (i.e. nitrous oxide turned off) till the time the patient was responding, ventilating spontaneously, orientated to time, place, and person, and able to be discharged from the recovery room, were all recorded. The requirements for narcotic reversal and post operative analgesia were also recorded for the first 90 min. Statistical analysis was performed with one way analysis of variance and co-variance. $P<0.05$ was considered significant.

RESULTS: Hemodynamic stability obtained from each group (H,F,A) are represented in the figures. No additional anesthetic agent was required in either A or F. Each blood pressure and heart-rate measure was counted as 1 observation and its percentage change from control was calculated. There were was no differences between groups in maintaining hemodynamic parameters within 20% of control. The recovery data is in the table. Time to respond to command was significantly shorter in A versus H. A significant number of patients required naloxone in group F but only 1 required more than a single dose.

FIGURE 1

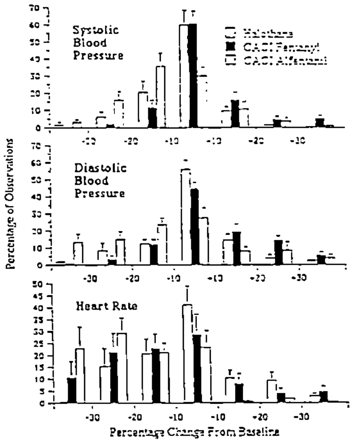

TABLE 1

		Halothane	Alfentanil	Fentanyl
Spont Vent.	(min)	3.8	7	6.5
Resp Cmd.	(min)	11.1	4.2	3.3
Extubation	(min)	5.1	7	7.5
Orientation	(min)	31.4	22.4	26.1
Discharge R.R.	(min)	129.5	100.2	142.6
Narcan	(patients)	-	2	5
N and V	(patients)	1	5	2
Analgesia Req. First 90 min.	(patients)	8/10	2/10	3/10

DISCUSSION: Good hemodynamic control and similar recovery was obtained in all groups. This study therefore demonstrated that anaesthesia produced by computer assisted infusion of alfentanil or fentanyl, was as good as inhalational anesthesia produced by halothane.

REFERENCES:

1. Alvis JM, Reves JG, Govier AV, et al: Computer-assisted continuous infusions of fentanyl during cardiac anesthesia: Comparison with a manual method. Anesthesiology 63:41-49, 1985.
2. Ausems ME, Stanski DR, Hug CC: Plasma concentrations of alfentanil required to supplement N_2O in surgical patients. Anesthesiology 63:A382, 1986.

TITLE: Assessment Of The Optimal Priming Dose For Atracurium, Pancuronium and Vecuronium To Obtain Rapid Onset Muscle Relaxation

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INTRODUCTION: The administration of a small sub-paralytic "priming dose" of a nondepolarizing muscle relaxant (NMR) followed by a larger "intubating" dose to speed the onset time of muscle relaxation has been popularized by Foldes as the "priming principle"[1]. At the present time the priming dose, priming interval, and intubating dose for the more commonly used nondepolarizing muscle relaxants have yet to be well defined. The current study was designed to 1) establish the optimal priming dose of vecuronium (V), pancuronium (P), and atracurium (A), 2) detect any difference among these three agents, and 3) compare their onset times to that of succinylcholine (S).

METHODS: After Instutional Review Board approval 160 ASA class I-III patients scheduled for elective surgery gave informed consent. Patients were randomly divided into four major groups (V,P,A,S). For each of the NMR studied, the patients were further divided into five subgroups of ten patients each according to the priming dose given i.e. no prime, 5%, 10%, 15%, or 20% of the total dose. The total dose for V was 0.08 mg/kg, P 0.1 mg/kg and A 0.6 mg/kg. The intubating dose, given 5 to 6 mins after the priming dose was the total dose minus the prime dose. The S group received 3 mg of d-Tubocurare as a prime and 1.5 mg/kg succinycholine. Patients were premedicated with diazepam, anesthesia was induced with thiopetal, maintained with 1 to 5 mcg/kg of fentanyl and N_2O/O_2. Following induction neuromuscular transmission (NMT) using a Puritan Benet NMT monitor was calibrated and the priming dose given. T1 and T_4% were monitored every 20 seconds for the initial 5 to 6 minutes following the priming dose. At five minutes, if NMT was stable the intubating cose of the relaxant was given and decay of NMT was recorded every 20 seconds thereafter. Statistical analysis was by analysis of variance and co-variance with repeated measures. $p<0.01$ was considered significant.

RESULTS: The maximal effect of the various primes on NMT for each NMR is shown in figures 1 - 3 (prime max). This effect was maximal for A 20% with a reduction in twitch height of 25%. This was significantly different from all other groups ($p<0.01$). When data for all three NMR groups were pooled the decay of NMT was significantly faster when a priming dose was used ($p=0.0002$). At 60 sec the degree of neuromuscular blockade from succinylcholine was significantly greater than any of the NMR regardless of prime, but at 80 sec (A15%) and 100 sec (A15%, V15%, p15%) this difference was no longer statistically significant (Fig 4).

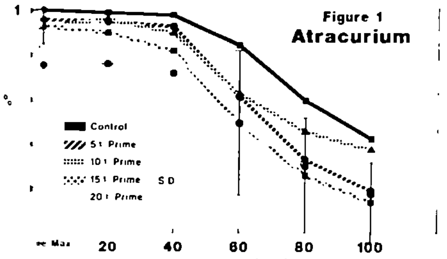
Figure 1
Atracurium

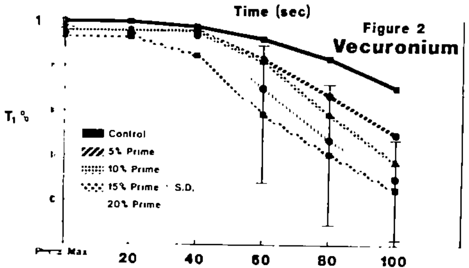
Figure 2
Vecuronium

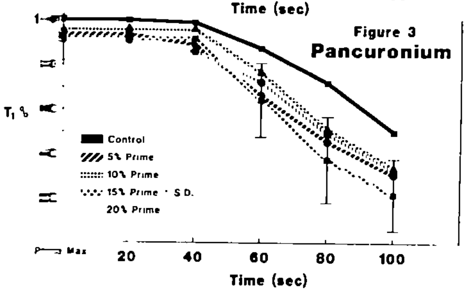
Figure 3
Pancuronium

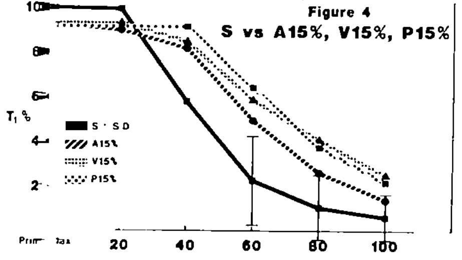
Figure 4
S vs A15%, V15%, P15%

DISCUSSION: Our data confirmed that priming effectively shortens onset time of muscle rlaxation. As can be noted from the graphs there was extreme patient to patient variability with all NMR, but this was much less prevelant in the S group. Patient variability therefore must be considered when using this technique. Our data indicate that the ideal priming doses for the NMR used are: V [illegible]5% (0.012 mg/kg,) A 15% (0.09mg/kg,) P 15% (0.015 mg/kg.) When the ideal prime for each NMR group were used, priming was as effective as S at 80 secs (A[illegible]5%) and 100 secs (A15%, V15%, P15%) but S was still superior at 60 secs.

REFERENCE

1. Fo[illegible]es FF, Schwartz S, Ilias W, et al. Rapid tracheal intubation with vecuronium: The priming principle. Anesthesiology 61:A294, 19[illegible]

Title: DOES VECURONIUM ACCUMULATE IN RENAL TRANSPLANT PATIENTS?

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Introduction: Several authors have stated that vecuronium(VEC) is useful in the patient with renal failure (1,2) while others believe atracurium(ATR) to be the muscle relaxant(MR) of choice (3). More recently, VEC accumulation has been described in the patient with renal failure (4). This might be clinically significant in the renal transplant patient who is essentially anephric and immune compromised where rapid recovery from neuromuscular block is desirable to allow early extubation. We are not aware of any study comparing ATR and VEC in the renal transplant patient. This study was designed as a trial of ATR and VEC with clinically useful doses in the cadaveric renal transplant patient.

Methods: After Institutional Review Board approval and informed consent, 14 ASA Class III patients undergoing cadaveric renal transplantation were studied. All patients were free of apparent uremic neuropathy and assigned randomly to receive either ATR or VEC. Premedication consisted of morphine sulphate 0.08 mg/kg and atropine 0.4 mg IM one hour prior to surgery. Induction consisted of thiopental 4-6 mg/kg IV followed by succinylcholine(SDC) 1.0 mg/kg to facilitate endotracheal intubation. Neuromuscular function was measured by recording the force of thumb adduction with a Grass FT10 force transducer. The ulnar nerve was stimulated after preloading with 250 grams, with a train of four every 10 seconds via 25 gauge subcutaneous electrodes and recorded on a Grass polygraph (Model 7). Electrodes were placed after induction and prior to SDC administration and baseline train of four was obtained. SDC was administered and time to maximum block was noted (SDC max). Maintenance of anesthesia consisted of isoflurane (ET concentration of 1.2% as determined by Beckman LB-3 end tidal Monitor) and fentanyl 4-6 µg/kg IV. After 90% recovery of T_1 from SDC (SDC 90%) either ATR (0.25 mg/kg) or VEC (0.05 mg/kg) were administered and the following times were noted: time to maximum block onset (REC max), injection to start of recovery, (start Rec) injection to 25% twitch recovery(REC 25%), injection to 75% (REC 75%) twitch recovery, injection to 90% (REC90%) recovery, time from 25-75% (REC 25-75) of twitch recovery as well as time from second dose to onset of maximum block (2nd dose max) and 90% , recovery after second dose(2nd dose 290%). At the conclusion of surgery neuromuscular blockade was antagonized with neostigmine 2.5 mg and glycopyrrolate 0.5 mg. One-way ANOVA was performed to determine significance of differences between the groups. A $p < 0.05$ was considered statistically significant. All values are expressed as mean ± standard deviation.

Results: The results of the study are summarized in Table 1. There was no significant difference between the two groups in age, weight, preoperative K^+, time from last dialysis or duration of surgery. There also was no difference in onset of SDC block, SDC90%, onset of NDP block and REC25%, 75% or 90% as well as maximum blockade achieved with a single dose of NDP. Furthermore, there was no significant difference between the two groups in the onset time after the second dose however, there was a significant difference in 90% recovery after the second dose of VEC as opposed to ATR ($p < 0.02$).

Discussion: Hunter, et al (1,4) combined the data from two separate studies of patient with renal failure and found no difference in the time of recovery(T_1 10%) from a single dose of VEC (0.1 mg/kg) or ATR (0.5 mg/kg), as well as recovery from incremental doses of VEC(0.04 mg/kg) or ATR(0.2 mg/kg). Similarly, we found no difference in patient's recovery after a single dose of ATR or VEC and after a 2nd dose of ATR. We did find however, that VEC does accumulate after a 2nd dose in the renal transplant patient. This would agree with the findings of Bevan et al (5), who demonstrated accumulation of VEC after achieving 95% blockade with 20-50 µg/kg boluses and at least 10 subsequent boluses of 10 µg/kg to maintain block.

The question whether isoflurane has a greater effect on ATR or VEC neuromuscular block has not been answered. We therefore maintained the same end tidal concentration of isoflurane in the two groups.

All patients were easily reversed with neostigmine and glycopyrrolate. Accumulation of MR is clinically relevant if one is to administer them indiscriminately without adequate monitoring and might be more significant in these patients who demonstrate accumulation with VEC.

TABLE 1

	Group 1(ATR) n=7	Group 2(VEC) n=7	P
SDC Max (mins)	1.4 ± .6	1.6 ± 0.4	NS
SDC 90 (mins)	12.5 ± 2.5	10.5 ± 4.4	NS
REC Max (mins)	3.2 ± 1.4	4.7 ± 3.6	NS
Start REC	19.4 ± 9.0	20.7 ± 6.8	NS
REC 25	34.5 ± 12	43.7 ± 33.6	NS
REC 75	51.1 ± 22.9	80.5 ± 67.3	NS
REC 90	58.5 ± 28.1	88.1 ± 68.0	NS
T_4/T_1 80% REC	69.8 ± 28.4	94.3 ± 56.0	NS
Max Block (%)	99.6 ± 0.9	97.6 ± 3.7	NS
25-75%	16.6 ± 12.8	37.1 ± 35.0	NS
2nd dose Max	2.0 ± 0.6	2.5 ± 0.6	NS
2nd dose 90%	54.0 ± 15.2	92.8 ± 5.9	< 0.02

REFERENCES

1. Hunter JM., et al. Comparison of Vecuronium, Atracurium and Tubocurarine in normal patients and in patients with no renal function. Br J Anaesth 1984;56:942-49.
2. Fahey MR., et al. Pharmacokinetics or ORG NC45 (Norcuron) in patients with and without renal failure. Br J Anaesth 1981;53:1049-53.
3. de Bros FM.,et al. Pharmacokinetics and pharmacodynamics of atracurium during isoflurane anesthesia in normal and anephric patients. Anesth Analg 1986;65:743-6.
4. Hunter JR, et al. Use of atracurium in patients with no renal function. Br J Anaesth 1982;54: 1251-58.
5. Bevan DR., et al. Cummulation of vecuronium in renal faiure. Anesthesiology 61:A296.

Title: LABETALOL FOR CONTROL OF POST CAROTID ENDARTEREYTOMY HYPERTENSION

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Introduction: Severe hypertensive episodes postoperatively can be associated with left ventricular failure, pulmonary edema, myocardial infarction, arrhythmia and cerebral hemorrhage (1). Postoperative hypertension is most likely to occur in the first 30 minutes with resolution in 4 hours in most instances (2). Postcarotid endarterectomy hypertension is a fairly common phenomenon with incidences as high as 56% (3) that can be associated with postoperative mortality and neurologic defect (4). Control of blood pressure (BP) in this patient population is desirable and labetalol may be a useful agent due to its combined α and β adrenergic blocking activity (5). We evaluated the use of intravenous labetalol for the control of hypertension in the post carotid endarterectomized patient.

Methods:Twenty-one ASA II-IV patients scheduled for elective carotid endarterectomy were studied with Institutional Review Board approval and informed consent. Patients were excluded on the basis of medical history that might contraindicate the use of β or α adrenergic blocking agents. Postoperative hypertension was defined as a supine systolic BP ≥ 200 mmHg and/or a diastolic BP ≥ 100 mmHg or a supine systolic BP ≥ 20% over the highest average preoperative systolic BP. Highest preoperative BP is the average of 3 consecutive BP measurements 1 minute apart after the patient rested quietly for 5 minutes. Patients were premedicated with morphine 0.08 mg/kg and atropine 0.4 mg IM. Induction utilized thiopental 4-6 mg/kg followed by succinylcholine 1 mg/kg for intubation. Maintenance was with fentanyl 4-6 μg/kg, N_2O/O_2 in a 60/40 ratio and isoflurane titrated to an inspired concentration necessary to maintain hemodynamic stability. The study commenced with cessation of isoflurane administration. The average of 3 consecutive BP measurements 30 seconds apart were monitored and recorded with a calibrated strip chart. EEG monitoring during the surgery and labetalol treatment and maintenance period was performed utilizing aperiodic analysis. Labetalol was administered once entrance BP criteria had been reached utilizing an initial bolus of 20 mg. and an additional injection of 40 mg over a 2 minute period every 10 minutes until a desired effect was obtained or a total maximum cummulative dose of 300 mg was administered. BP and heart rate (HR) was determined immediately before, 5 and 10 minutes after each injection until goal BP was reached and maintained for 15 minutes. Goal BP was defined as a BP ≤ 10% above the highest average preoperative BP or a systolic BP ≤ 150 mmHg. Afterward BP was recorded every 15 minutes for 1 hour and observed for 2 more hours at 30 minute intervals. No concomittant diuretic or antihypertensive therapy was utilized during the study period. Changes in BP before and after labetalol were analyzed by paired t test. A p value < 0.05 was considered statistically significant.

Results: Twenty-one patients were entered into the study with 10 developing BP high enough for treatment with labetalol. Eight had a history of hypertension (mean age was 66.0 ± 7.1 with 5 male and 5 female). Eight patients required a single 20 mg injection of labetalol, 1 required a total dose of 60 mg and 1 required 100 mg. All patients reached and maintained their goal BP during the maintenance period and required no further intravenous medication for BP control during the first 24 hours postop. Table I demonstrates control, pre and post treatment (Rx) BP values. Statistically significant decreases in systolic, diastolic and mean arterial pressure was noted when goal BP was reached as well as 5, 10, 30, 60 and 120 minute after labetalol Rx as compared to pre Rx BP. There was no statistically significant difference in HR at any Rx time. No patients became hypotensive and no adverse electroencephalographic changes were noted after labetalol treatment.

Discussion:Labetalol has been demonstrated to be a useful agent for the reduction of BP in severe hypertension crisis (6). The β to α adrenergic blocking activity ratio is 7:1 with an onset of action in 1-2 minutes and maximum effect in 10 minutes and an elimination ½ life of approximately 5 hours. As compared to an equal antihypertensive dose of propranolol, there is a slight decrease in HR with minimal if any effect on normal cardiac output (5). We utilized the same dose as described in those studies on non surgical hypertensive cases and found this to be a useful and effective treatment. The response was rapid, well maintained, with no demonstrated side effects or deliterious effect on the EEG.

Table 1

	Preop Baseline	Immediate Pre Labetalol	Immediate Post Labetalol
BP Sys	142.2±19.1	181.2±20.8	147.7±19.5
BP Dis	78.0±9.7	85.7±16.6	68.4±10.9
MAP	99.4±10.5	117.5±15.5	94.8±12.1
HR	81.3±13.4	83.6±18.5	70.4±9.8

	10 min. post Labetalol	30 min. post Labetalol	2 hrs. post Labetalol
BP Sys	148.6±22.5	143.1±19.4	137.4±15.1
BP Dis	76.8±13.4	61.7±12.2	60.2±11.5
MAP	97.4±14.1	89.8±11.9	85.9±11.1
HR	70.4±9.8	66.0±7.8	70.2±11.0

$p < 0.001$ baseline vs immediate pre Rx BP
$p < 0.002$ immediate vs all post Rx BP

REFERENCES

1. Gal TJ, Cooperman L: Br J Anaesth 1975;47:70-4.
2. Goodloe SL: in Stoelting RK, Dierdorf SF ed: Anesthesia and Coexisting disease N.Y. Churchill Livingstone 1982;99-17.
3. Lehr MS, Salzman EW, Silen W: Stroke 1970;1: 307-13.
4. Towne JB, Bernhard UM: Surgery 1980;88:575-80.
5. Carter BL: Labetalol. Drug Intelligence & Clinical Pharmacy 1983;17:704-12.
6. Cressman MD et al: Am Heart J 1984;107:980-85.

Title: TRANSTRACHEAL VENTILATION FOR COMPLETE UPPER AIRWAY OBSTRUCTION IN PIGS

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Introduction. Percutaneous transtracheal ventilation is a lifesaving procedure in severe upper airway obstruction. Intermittent jets of oxygen provided good ventilation through a 14 g needle or catheter (1.47 mm ID) (1,2). However, in complete airway obstruction this technique has the potential to severely increase tracheal pressure and barotrauma. An alternative is to use larger bore cannulas (2.5 mm ID with oxygen and 3.0 mm with air) with a bag-valve assisted respiration (3). In this study we evaluated a standard 10 g catheter (2.4 mm I.D.) and a new portable Venturi device (PVD) that delivered positive pressure.

Methods Thirteen pigs, each weighing 27 to 41 kg, were used to simulate the human model. General anesthesia was induced with ketamine 30 mg/kg and promazine 3 mg/kg IM; it was maintained with an infusion of pentobarbital 4 mg/kg/hr IV. The trachea was intubated with a cuffed oral tube. Animals were monitored using pulmonary artery and arterial catheters for blood gas analysis and pressure measurement. A catheter was placed in the lower end of the trachea to measure airway pressure. Baseline measurements were recorded while the animals breathed air. The control group (Group I, n = 5) spontaneously breathed 100% oxygen for six minutes, after which muscle paralysis was induced with succinylcholine 1.5 mg/kg IV. After the pig stopped breathing, the tracheal tube was occluded. The protocol and anesthesia for Group II (n = 8) was similar to group I up to and including the point of tracheal occlusion. At this point ventilation was instituted using a 10 g catheter (ID 2.4 mm) inserted through the tracheal wall distal to the end of the endotrachael tube and connected to the PVD with a standard 3.0 mm endotracheal tube connector. The PVD (Percussionaire Corp.) used oxygen from a 50 psi source, and delivered an FIO2 between 0.68-0.92. At operating pressures, the PVD delivered inspiratory flows up to 100 LPM and oscillated at about 0.5 Hz. After 16 minutes of ventilation the plug was removed from the tracheal tube and the animal was ventilated with a Harvard pump until it resumed spontaneous ventilation; then the entire procedure was repeated two or three times for each animal. Data were recorded every 30 seconds for the first five minutes and every minute thereafter or until cardiovascular collapse occurred.

Results Results are summarized in Table I. In group II, all replicates of the same animal were averaged. Asphyxia produced cardiorespiratory failure in every animal in group I in less than six minutes. At five minutes PaCO2 and mean pulmonary artery pressure increased significantly while PaO2 decreased significantly. In contrast, group II showed marked cardiovascular stability. Throughout the experiment, mean systemic arterial pressure was comparable to baseline but showed a small decline after 16 minutes of ventilation. The mean pulmonary artery pressure followed a similar trend. Heart rate remained stable. Peak airway pressure showed a constant peak value of 14 cm H2O and an end-tidal value of 5-7 cm H2O. Animals maintained normal values of PaCO2 and pH. PaO2 showed a steady increase in every animal over time.

Discussion. The PVD controlled ventilation with an adequate gas exchange when we used a 2.4 mm I.D. transtracheal catheter (standard 10 g angiocath). Treated animals showed a remarkable stability in cardiorespiratory parameters. The concurrent presence of continuous positive airway pressure as a baseline airway pressure of 5-7 cm H2O and the low oscillation may explain that the PaO2 is much higher than previously reported (range 96-78 torr with oxygen) using a larger orifice (3). This finding reinforces the hypothesis that a transtracheal orifice of 2.4 mm ID and an appropriate flow-interrupted cycle are critical to assist or control ventilation during complete upper airway obstruction.

References

1. Klain M, Brian Smith R: High frequency percutaneous transtracheal jet ventilation. Crit. Care Med. 5: 280-287, 1977.
2. Swartzman S, Wilson MA, Hoff BH, et al.: Percutaneous transtracheal jet ventilation for cardiopulmonary resuscitation - evaluation of a new jet ventilator. Crit. Care Med. 12: 8-13, 1984.
3. Neff CC, Pfister RC, Van Sonnenberg E: Percutaneous transtracheal ventilation - experimental and practical aspects. J Trauma 23: 84-90, 1983.

TABLE I

		Baseline	Seconds after tracheal occlusion		
			90	300	960
pH	group 1	7.39 ±.03	7.42 ±.06	7.33 ±.05	-
	group 2	7.37 ±.05	7.36 ±.06	7.37 ±.07	7.41 ±.07
PaCO2 (mmHg)	group 1	36 ±14	36 ±4	52 ±3*	-
	group 2	38 ±3	43 ±5	41 ±5	39 ±6
PaO2 (mmHg)	group 1	72 ±9	192 ±27	13 ±5**	-
	group 2	89 ±10	333 ±54	461 ±41	500 ±59
HR (beats/min)	group 1	98 ±16	96 ±16	124 ±4	-
	group 2	116 ±23	115 ±28	113 ±24	107 ±19
MAP (mm Hg)	group 1	89 ±18	94 ±18	62 ±19	-
	group 2	101 ±12	94 ±8	86 ±11	85 ±12
MPAP (mm Hg)	group 1	16 ±2	12 ±3	25 ±4*	-
	group 2	20 ±3	24 ±4	21 ±3	19 ±3

HR = heart rate
MAP = mean arterial pressure
MPAP = mean pulmonary arterial pressure
Comparison between data at 90 sec and 300 sec after occlusion: * = $p<0.05$ and ** $p<0.001$
mean ± SD

Title: **THE EFFECTS OF PEEP ON CANINE DIAPHRAGMATIC LENGTH**

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Introduction. Positive end expiratory pressure (PEEP) breathing is known to increase lung volume from its resting position (functional residual capacity, FRC), but this may be counterbalanced by increased tone in the abdominal muscles because positive pressure breathing increases abdominal muscle contraction during expiration. Therefore FRC changes are less or the ribcage compartment is affected more (1) than the abdominal compartment (i.e., diaphragm) due to the increased abdominal muscle tone. Since diaphragm length is coupled to abdominal volume, abdominal muscle contraction is anticipated to lengthen the diaphragm. We tested this hypothesis by using a new technique to measure costal (cos) and crural (cru) diaphragmatic length at different levels of PEEP.

Methods. Diaphragmatic length was measured by sonomicrometry in six dogs anesthetized with 30mg/kg of pentobarbital and intubated with a cuffed endotracheal tube (ET). The sonomicrometer was a four-channel ultrasonic device (Triton Technology, San Diego, CA) that measures distance between pairs of small transducers which consist of a ferroelectric ceramic plate covered with a biconvex polyester diverging lense (2mm diameter). The transit time of the ultrasonic wave is proportional to the length of muscle. Dogs were breathing spontaneously 40% O2 through a one-way Hans-Rudolph valve and the exhalation line placed under water at different levels to adjust for 4-8-12 and 16 cm H2O of PEEP. A mass spectrometer monitored FIO2 and end tidal CO2. Tidal volume (VT) was obtained from the integrated flow signal. Abdominal pressure (Pab) was measured by a 5 cm latex balloon placed in the subphrenic space. Airway pressure (Pao) was recorded at a side port on the ET and reflected actual PEEP. In addition to length changes, electromyograms (EMG) of both the costal and crural portion of the diaphragm were obtained. At each level of PEEP, control measurements of Pab, VT, EMG, and tidal shortening as per cent of resting length at FRC (% LFRC) were repeated when breathing had become regular. At the end of the experiment the animal was paralyzed with atracurium (0.5 mg/kg), passively inflated to total lung capacity, and the diaphragm length changes at different Pao were recorded.

Results and Discussion. Table 1 shows the significant increase in abdominal muscle activity with the level of PEEP. The resting length of the diaphragm at end expiration (where the effect of PEEP is maximal) is shown in Table 2. This suggests that abdominal muscle contraction significantly increases the resting length of both parts of the diaphragm and increases FRC primarily by expansion of the lower rib cage. Increased length during passive inflation at identical airway pressure is compatible with the lack of abdominal tone. Since the VT was unchanged and the active shortening of the diaphragm during tidal breathing increased significantly from 10 ± 2.1 %LFRC (at zero PEEP) to 17 ± 2.1 %LFRC (at PEEP 16) for cru and from 9.6 ± 2.4 %LFRC (at zero PEEP) to 14 ± 3.0 %LFRC (at PEEP 16) for cos the diaphragmatic contribution to tidal volume increased at higher lung volumes. Optimum muscle length in relation to generated pressure is about 5% below LFRC (2) for costal diaphragm, therefore PEEP in the range of 4-8 cm H2O may still preserve optimum force output. However, increasingly less shortening is seen with stimulation at higher lung volumes.

References.
1. DeTroyer A, Sampson M, Sigrist S, Kelly S. How the abdominal muscles act on rib cage. J Appl Physiol 54: 465-469, 1983.
2. Road J, Newman S, Derenne JP, Grassino A. In vivo length-force relationship of canine diaphragm. J Appl Physiol 60: 63-70, 1986.

Table .

	PEEP cmH20			
	4	8	12	16
Pab cmH20	1.5 ± 0.3	3.2 ± 0.4	4.0 ± 0.3	5.8 ± 0.6

mean ± SEM

Table 2.

	%LFRC cru		%LFRC cos	
	end-expiration	paralysis	end-expiration	paralysis
PEEP 8 cmH20	4.3 ± 2.6	7.2 ± 2.6	3.2 ± 0.6	5.3 ± 1.8
PEEP 16 cmH20	8.5 ± 2.0	15.0 ± 4.0	4.9 ± 0.9	13.0 ± 3.0

mean ± SEM

Title: Lumbar Epidural Morphine and Prophylactic Naloxone Infusions for Post-Thoracotomy Analgesia: Effects on Quality of Analgesia and Side Effects

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Introduction: Lumbar epidural administration of morphine has been shown to be effective in providing post-thoracotomy analgesia (1), and reports suggest that naloxone is effective in the reduction of side effects without concurrent loss of analgesia (2,3). To examine the effects of naloxone after prophylactic lumbar epidural morphine for post-thoracotomy analgesia, a double-blind, randomized, placebo-controlled pilot study was initiated with the objectives of examining 1) the quality of analgesia and 2) the incidence of side effects obtained with each dose regimen.

Methods: Twenty four patients scheduled for thoracotomy as a result of pulmonary disease gave informed consent. The protocol was approved by our Human Research Committee. The patients were instructed preoperatively in scoring the visual analogue scale (VAS). Premedication was with oral diazepam and a standard anaesthetic technique was employed using thiopental, isoflurane and fentanyl supplementation (2-5µg/kg). A lumbar epidural catheter was inserted and placement confirmed prior to induction. Preservative-free morphine sulphate (0.1 mg/kg) was administered with the patient supine as soon as possible after confirmation of catheter placement. Patients were randomly assigned to one of the four study groups.

Group	Single I.V. Bolus	Continuous Infusion X 24 Hours
I	Normal Saline	Normal Saline
II	Naloxone 0.4 µg/kg	Naloxone 0.4 µg/kg/h
III	Naloxone 2.0 µg/kg	Naloxone 2.0 µg/kg/h
IV	Naloxone 4.0 µg/kg	Naloxone 4.0 µg/kg/h

Postoperative analgesia was provided with intravenous morphine in 1 mg increments as required. Prior to the start of study medication, VAS scores were recorded and repeated hourly (while awake) for 24 hours. Side effects were recorded. One hour after arrival in Recovery Room, each patient received, a single, slow, intravenous bolus followed within thirty minutes by a continuous infusion. The volumes for the bolus and continuous infusion were standardized across study groups.

Primary efficacy variables were: 1) total amount of intravenous morphine administered; 2) longest interval between analgesics and 3) VAS. Statistical significance was evaluated by one way analysis of variance with a p value = 0.05.

Results: The study population consisted of 18 men and 11 women. Differences in age, height or weight between the groups were not significant.

There were no significant differences between groups for any of the three primary efficacy variables. However, definite trends appeared for all efficacy variables with the placebo group having the best mean scores.

Group	N	I.V. Morphine	Longest Interval Between Analgesia	VAS
I	7	23.6 mg	436.4 min	33.2
II	8	23.4 mg	375.6 min	37.1
III	7	27.0 mg	247.9 min	47.5
IV	5	30.4 mg	115.0 min	54.9
p		$< .25$	$.10 < p < .25$	$.10 < p < .25$

Three patients had their study medication discontinued because of moderate to severe pain that was uncontrollable with intravenous morphine. These three patients belonged to the high dose naloxone group and consequently this group was not continued beyond the five patients. There were no significant differences nor were any trends noted, in the incidences of respiratory depression, nausea and vomiting, pruritus or urinary retention between groups.

Discussion: Two recent reports have suggested naloxone infusions might be useful in the prevention of side-effects associated with epidural morphine, without affecting analgesia (4,5). Both used a lower dose of epidural morphine and a higher naloxone infusion concentration. It is apparent from the results of our pilot study that analgesia was detrimentally affected by prophylactic naloxone infusions in the dose range studied. Side effects of epidural morphine were not decreased. Because of the small numbers in each group, statistical analysis failed to show significant differences in the efficacy variables. However our clinical observations and the trends in pain experienced, convinced us that this particular technique cannot be recommended.

References:

(1) Fromme GA, Steidl LJ and Danielson DR: Comparison of lumbar and thoracic epidural morphine for relief of post-thoracotomy pain. Anesth. Analg 1985; 64: 454.
(2) Jones RD and Jones JB: Intrathecal morphine: naloxone reverses respiratory depression but not analgesia. Br. Med. J. 1980; 281: 645.
(3) Brookshire GL et al: Effects of naloxone on the mother and the neonate after intrathecal morphine for labour and analgesia. Anesth. 1983; 59: A417.
(4) Rawal N, Schott U, Dahlstrom B, Inturrisi CE, Tandon B, Sjostrand U and Wennhager M: Influence of naloxone infusions on analgesia and respiratory depression following epidural morphine. Anesth 1986; 64: 194
(5) Thind GS, Wells JCD and Wilkes RG: The effects of continuous intravenous naloxone on epidural morphine analgesia. Anaesth 1986; 41: 582

Title: MATERNAL HEMODYNAMIC EFFECTS OF EPHEDRINE AND PHENYLEPHRINE

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Pure alpha agent phenyephrine(Phen) is not used to treat maternal hypotension because it may increase blood pressure (BP) without increasing the cardiac output (Q). Ephedrine (Eph) with alpha and beta action is preferred.This study compares maternal hemodynamic changes with Eph or Phen therapy used for maternal hypotension caused by lumbar epidural anesthesia (LEA)

Methods: The study was approved by the review board.Patients gave informed consent.Fifty-two healthy patients scheduled for elective cesarean section (age 31÷5,weight 69+5 kg) were given 1200 ml Ringer lactate i.v..LEA was induced to T6 level by injecting 5 ml increments of 1.5% lidocaine with 1:200,000 epinephrine through a L3-L4 catheter. The uterus was displaced to the left.An impedance cardiograph was used to measure stroke volume (SV),preejection period (PEP) and ventricular ejection time (VET).PEP was measured from the onset of Q wave of the EKG to the onset of ventricular ejection on the dZ/dT tracing (point X).VET was measured from point X to the the the second heart sound on the phonocardiogram.Gerrad's formula was used to calculate ejection fraction: EF=1.125-1.25 PEP/VET[1].End diastolic volume (EDV) was calculated by dividing SV by EF.Systemic vascular resistance (SVR) was calculated from mean BP (BP) and Q. Any systolic pressure <100 torr was treated with 5 mg Eph or with 100 ug Phen,selected randomly (n=12 in each group).The remaining 28 did not require vasopressor (Controls).Results were expressed as mean+ 1SE. Analysis of variance and t-test were used for statistics.

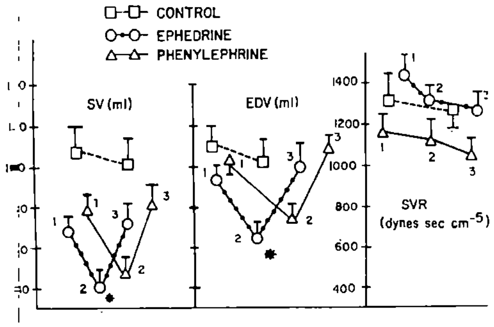
Results: Neonatal Apgar scores and umbilical cord blood acid-base status did not differ among the groups.Baseline SV,Q,EDV,BP,HR,SVR and EF were similar in the groups.In control subjects only heart rate (HR) increased significantly at T6 (Table and Figure).In both hypotensive groups HR increased but BP,VET,EF,SV,Q and EDV were reduced during hypotension.Eph and Phen restored them to near normalcy.SVR did not differ significantly from the baseline values either during hypotension or after treatment with Phen or Eph (Fig).

Conclusions: Data show that hypotension due to LEA is associated with decreased EDV (preload) with litle change in SVR.The decreased preload was probably due to venous pooling caused by sympathectomy.Increased preload after vasopressor therapy suggests constriction of the capacitance bed.Thus at the doses studied both Eph and Phen increase BP by similar mechanisms (i.e. increased preload). The minimal change in EF seen after vasopressor therapy suggests only minor ionotropic effect. Phen therapy was not associated with an increase in after load Both Eph and Phen probably caused decreased HR by baroceptor reflex.

TABLE: NORMOTENSIVE PATIENTS (n=28)

	HR	BP (torr)	VET (Sec)	PEP	EF	Q (L/min)
Base line	80	90	0.32	0.08	0.65	5.5
	(2)	(3)	----(0.01)-----			(0.3)
T6	98*	89	0.28	0.07	0.65	5.9
	(5)	(3)	----(0.01)------			(0.[illegible])
EPHEDRINE (N=12)						
Base line	79	90	0.32	0.07	0.67	5.[illegible]
	(3)	(3)	----(0.01)------			(0.3)
Hypotension	107*	67*	0.19*	0.06	0.59*	4.3*
	(5)	(2)	----(0.01)------			(0.04)
Post Rx	87	87	0.28	0.07	0.66	5.8
	(10)	(3)	-----(0.01)-----			(0.4)
PHENYLEPHRINE (n=12)						
Base line	80	83	0.31	0.06	0.7	6.1
	(3)	(2)	-----(0.01)------			(0.3)
Hypotension	99*	62*	0.22*	0.06	0.64*	4.7*
	(6)	(2)	-----(0.01)------			(0.4)
Post Rx	79	82	0.31	0.07	0.7	6.7
	(2)	(2)	----(0.01)-----			(0.6)

*-significantly different from baseline and posttreatment values.



Legend for figure: 1=baselinen,2=during hypotension,3=after vasopressor; *- differnt from 1 and 3 ($p<0.01$).

Reference:

1)Gerrad CL et al: Circulation 42:455-462,1970

Title: EFFECTS OF ISOFLURANE ON THE HYPERDYNAMIC CIRCULATION OF BURNED PATIENTS

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Introduction: Patients with severe burns develop a hyperdynamic state characterized by a cardiac output (CO) 1.5-3 times higher than normal, tachycardia and low systemic vascular resistance (SVR) (1). This state results from an increased metabolic rate, anemia, and the development of a highly perfused vascular bed in the burned areas. Isoflurane, in normal subjects, has been shown to maintain CO and to decrease arterial blood pressure mainly by decreasing SVR (2). This study was designed to test the hypothesis that isoflurane does not depress the hyperdynamic circulation in burned patients.

Methods: After IRB approval, 7 patients with major burns undergoing debridement and skin-grafting procedures were studied. All patients were without significant cardiac, pulmonary, hepatic or kidney dysfunction and were not septic. Patients' mean ± SD age was 36 ± 7 yrs, body weight 82 ± 15 kg, burn size 46 ± 10% body surface area (BSA), postburn day of study 10 ± 9. Two patients were studied on two different occasions, 2 and 14 days apart, respectively. Pulmonary and systemic arterial catheters were inserted under local anesthesia and intravenous sedation with diazepam 5 mg and fentanyl 0.1-0.25 mg. Anesthesia was induced with thiopental 4-6 mg/kg, followed by vecuronium 0.1 $mg{\cdot}kg^{-1}$ to facilitate intubation and maintained with N_2O 60% in oxygen and isoflurane at an end-tidal concentration of 0.7-0.9%, measured by mass spectrometry. Isoflurane and nitrous oxide concentrations were chosen to achieve a total potency of 1.3 MAC. Ventilation was controlled to maintain $PaCO_2$ within normal limits. Ringer's lactated solution and blood were administered to keep pulmonary capillary wedge pressure (PCWP) within normal range and hematocrit (Hct) approximately 30%. HR, mean arterial pressure (MAP), CO, PCWP, right atrial pressure (RAP), Hct, arterial and mixed venous blood gases and oxygen content were measured before induction of anesthesia (Stage I, baseline); after induction, when desired end-tidal isoflurane concentration had been kept constant at least 15 minutes (Stage II); after end of surgery but still under anesthesia (Stage III); in the recovery room 1 to 3 hours after anesthesia (Stage IV). Cardiac index (CI), stroke volume index (SVI), and SVR were calculated using standard equations. Total body oxygen consumption ($\dot{V}O_2$) was calculated by the Fick equation. Statistical analysis was performed using student's t-test for paired data; $p < 0.05$ was considered significant.

Results: All patients were in a hyperdynamic-hypermetabolic state. Hemodynamic and metabolic effects of isoflurane anesthesia are summarized in Table 1. No significant differences were detected between Stage II and Stage III. After anesthesia, when the patients were awake and breathing spontaneously in the recovery room (Stage IV), all variables were back to baseline values. Baseline (Stage I) pH was 7.43 ± 0.02, $PaCO_2$ was 37.4 ± 5 mmHg, and Hct was 30% ± 3.5% and did not change throughout the study period.

Discussion: Isoflurane decreased CI by decreasing both HR and SVI. However, the decrease in SVI was statistically significant only at Stage II. The already low SVR did not change and the decrease in MAP was proportional to the decrease in CI. These changes are different from those reported in normal subjects in whom isoflurane decreased MAP mainly by affecting SVR and maintained CO close to normal values by increasing HR (2). Following induction, the high $\dot{V}O_2$ decreased approximately 50%, approaching the value reported for unburned anesthetized patients (2). The concomitant decrease in CI was associated with a decrease in $AVDO_2$ and no evidence of metabolic acidosis, suggesting that the change in CI was a consequence of the reduced metabolic requirements. CI decreased proportionally less than $\dot{V}O_2$ (32% vs 50%), indicating that under isoflurane anesthesia total body oxygen supply-demand balance was well maintained. The posed hypothesis is rejected: isoflurane, even at moderate concentrations, decreased CO in burned patients. However, the decrease in CO was associated with a parallel decrease in $\dot{V}O_2$ so that at all times an adequate total body oxygen supply-demand balance was maintained, suggesting that isoflurane can be safely used in anesthetizing hyperdynamic burned patients.

Table 1.
CARDIOVASCULAR EFFECTS OF ISOFLURANE
IN BURNED PATIENTS (Mean ± SD)

Variable	STAGE I	STAGE II	STAGE III
HR	126 ± 13	110 ± 12^+	100 ± 114^+
MAP	92 ± 19	64 ± 7^+	65 ± 8^+
CI	6.5 ± 0.9	4.6 ± 0.7^+	4.7 ± 0.6^+
SVI	52 ± 10	42 ± 9*	47 ± 11
SVR	536 ± 176	506 ± 107	496 ± 131
PCWP	12 ± 2.0	10 ± 2.6	10 ± 2.6
RAP	9 ± 2.0	8 ± 3.1	9 ± 2.4
$AVDO_2$	3.4 ± 0.4	2.6 ± 0.6*	2.3 ± 0.5^+
$\dot{V}O_2$	221 ± 40	120 ± 25^+	106 ± 13^+

Stages I-III (see text for explanation). HR = heart rate (bpm), MAP = mean arterial pressure (mmHg), CI = cardiac index ($l{\cdot}min^{-1}{\cdot}m^{-2}$), SVI = stroke volume index ($ml{\cdot}beats^{-1}{\cdot}m^{-2}$), SVR = systemic vascular resistance ($dynes{\cdot}sec^{-1}{\cdot}cm^{-5}$), PCWP = pulmonary capillary wedge pressure (mmHg), RAP = right arterial pressure (mmHg), $AVDO_2$ = arterio-venous oxygen difference ($ml{\cdot}dl^{-1}$), $\dot{V}O_2$ = total body oxygen consumption ($ml{\cdot}min^{-1}{\cdot}m^{-2}$). * $p < 0.05$, + $p < 0.01$.

References:

1. Gump FE, Price JB Jr, Kinney JM: Blood flow and oxygen consumption in patients with severe burns. Surg Gynecol Obstet 1970;130:23-28.
2. Dolan WM, Stevens WC, Eger EI II, et al: The cardiovascular and respiratory effects of isoflurane-nitrous oxide anesthesia. Can Anaesth Soc J 1974;21:557-568.

Title: INTRAVENOUS REGIONAL ANESTHESIA: EFFECT OF TOURNIQUET SIZE AND TYPE ON LEAKAGE UNDER THE TOURNIQUET

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Introduction: Intravenous regional anesthesia has been associated with toxic symptoms, cardiac arrest, and even death.[1] It has been shown[2] that venous pressure during injection can equal or exceed the effective tourniquet pressure (TP), thereby allowing injected solution to leak under the tourniquet and into the general circulation. The effective TP is the pressure transmitted to the underlying arteries and veins of the arm. Previous work[2] has demonstrated that the effective TP with a double tourniquet averages 80-100 mmHg less than the registered intracuff TP. That study, however, utilized the common practice of inflating only the proximal cuff at the time of injection. The main factor relating effective TP to intracuff (gauge) TP is the width of the tourniquet in relation to the size of the limb. Double tourniquets are advantageous and commonly used during intravenous regional anesthesia, but by anatomic necessity each cuff can only be 5-6 cm wide. Inflation of both cuffs during injection may provide a higher effective TP. This has not to date been evaluated. Deflation of the distal cuff a few minutes after injection would preserve the capability of later relieving intraoperative tourniquet pain, and still provide additional protection from leakage during injection. The purpose of this study was to investigate the relationship between the intracuff (gauge) pressure and the effective TP for three different tourniquet types.

Methods: Following approval by the Clinical Research Practices Committee and after informed consent was obtained, we inserted two 20 g. catheters in the antecubital veins of ten healthy volunteers. We measured venous pressures through one catheter, and injected saline solution through the other. Three injections of 50 ml of saline were made over 20-25 seconds with a different tourniquet for each injection. A five minute rest period between injections was adequate to allow identical results to be obtained during repetitive testing of selected volunteers. A wide tourniquet (13 cm sphygmomanometer cuff - termed BP cuff), a double tourniquet (Zimmer Inflato-Matic, each cuff 6.1 cm wide) with the proximal cuff inflated (termed DBL 1), and the same double tourniquet with both cuffs inflated (termed DBL 2) were used in random order. All tourniquets were inflated to an intracuff (gauge) pressure of 300 mmHg. Venous pressure curves were obtained during injection for the different tourniquet types. Data is presented as mean ± SE and was analyzed by one way analysis of variance followed by paired t-tests, with $p<0.01$ considered significant. Previous data[2] using xenon-133 revealed that leakage of solution under the tourniquet coincides with the presence of a venous "plateau" or "leakage" pressure, and that the rapid 50 ml antecubital injection without prior exsanguination would produce a leakage pressure in all volunteers. The leakage pressure is the maximum venous pressure obtainable during injection.

Results: Leakage pressures were obtained with all injections. The BP cuff provided the highest leakage pressure (i.e. - best protection against leakage), and was significantly greater than with DBL 2 or DBL 1 (table 1). The leakage pressure for DBL 2 was significantly higher than for DBL 1. The maximum improvement of leakage pressure for DBL 2 as compared to DBL 1 was 26 mmHg. Two subjects differed in these values by <2 mmHg. Venous pressure in all subjects decreased to <100 mmHg within one minute after completion of the injection. Venous pressure equilibrated to approximately 40 mmHg by several minutes after injection.

Discussion: At the same intracuff pressure, the data indicate that the BP cuff provides greater protection against leakage than either DBL 1 or DBL 2. Despite similar overall widths, DBL 2 is clearly not equivalent to the BP cuff. Between DBL 1 and DBL 2, the use of DBL 2 provides a statistical improvement in effective TP. Two of the ten subjects, however, had nearly identical leakage pressures for DBL 1 and DBL 2. The rapid decline for all subjects in venous pressure after injection indicates that deflation of the distal tourniquet several minutes after injection would not be associated with a risk of venous leakage. Venous pressure should still be high enough to cause diffusion and resultant anesthesia under the distal tourniquet. The use of this technique in combination with other techniques previously reported[2] should help to avoid leakage of injected anesthetic solution under the tourniquet. The sequential use of double tourniquet cuffs allows relief of intraoperative tourniquet pain, but anesthesiologists should be aware of the potential shortcomings of this tourniquet type. The effective TP of a double tourniquet with the proximal cuff inflated averages nearly 80 mmHg less than the gauge pressure, and can usually be moderately improved by simultaneous inflation of the other cuff. By avoiding leakage and keeping the anesthetic isolated in the limb, one would expect a decrease in the incidence and severity of toxic symptoms, and an increase in the percentage of successful blocks.

Table 1: Tourniquet Types and Leakage Pressures

Tourniquet Type	Intracuff (gauge) pressure (mmHg)	Leakage Pressure (mmHg)
BP cuff	300	294 ± 2
DBL 2 cuff	300	236 ± 3
DBL 1 cuff	300	224 ± 4

References:

1. Heath ML: Bupivacaine Toxicity and Bier Blocks. Anesthesiology 59:481, 1983.
2. Grice SC, Morell RM, Balestrieri FJ, Stump DA, Howard G: Intravenous Regional Anesthesia: Evaluation and Prevention of Leakage Under the Tourniquet. Anesthesiology 63:A221, 1985.

TITLE: ALFENTANIL IS NOT A COMPLETE ANESTHETIC IN DOGS

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Introduction. Narcotic analgesics (NA) are limited in their ability to reduce enflurane MAC in the dog (ceiling effect).[1] Controversy exists about the interpretation of these observations, especially since NA are widely used as anesthetics in man. The plasma concentration vs anesthetic effect relationships have been defined for alfentanil (Alf) in human patients.[2] This study was done to define the alfentanil concentration vs anesthetic effect relationship in the dog using MAC reduction as the model

Methods. Fasting mongrel dogs ($n=10$) weighing 16 ± 1 kg (Mean ± SEM) were each given succinylcholine 100 ug/kg and atropine 100 ug/kg and anesthesia was induced with 5% enflurane (Enf). Following tracheal intubation, mechanical ventilation maintained arterial blood gases in the normal range. Ringers lactate solution (12 ± 0.5 ml.kg$^{-1}\cdot$min^{-1}) was infused and body temperature was maintained within ± 1.5°C. Heart rate and rhythm, urinary output, and end-tidal enflurane concentration were monitored. Alfentanil arterial plasma concentration [ALF] was determined by radioimmunoassay. After determination of control enflurane MAC (EMAC) as previously described[1] all but one animal received at least four consecutively increasing infusions rates of Alf (Table). A priming infusion was administered over 20 min prior to each maintenance infusion. After a one-hour stabilization period, EMAC was again measured for each infusion rate. [ALF] was determined 45 min after the start of each new infusion rate and then every 15 min until EMAC was determined. The differences between EMAC reductions were evaluated by Student's T-test.

Results. Progressively increasing infusion rates (x) produced incremental increases in [ALF] = 38x - 39, $r=0.999$. However a ceiling effect was observed for EMAC reduction (Table). The lowest infusion rate produced an EMAC reduction of 24% at an [ALF] of 17 ng/ml. The average peak EMAC reduction was 70 ± 3% with an infusion rate of 32 ug.kg^{-1}.min^{-1} and an [ALF] of 1150 ± 142 ng/ml but this degree of EMAC reduction was not statistically different from that produced by an infusion rate of 8 ug.kg^{-1}.min^{-1} (69 ± 6.0% EMAC reduction at 223 ± 13 ng/ml).

Discussion. Alf at progressively increasing dose-rates produced a concentration-dependent reduction of EMAC but a ceiling effect was evident. Of significance is the observation that the degree of MAC reduction produced by Alf (69% at 8 ug.kg^{-1}.min^{-1}) is not unlike that produced by fentanyl (65% at 0.8 ug.kg^{-1}.min^{-1}) at plasma concentrations of 223 and 30 ng/ml respectively. This potency ratio is similar to that found in man (7-10:1) although Scott el al. found a plasma concentration ratio of 75:1 (Alf:F) for an equivalent hypnotic effect documented by changes in the EEG.[3] Could it be that there is a different plasma concentration potency ratio for sleep vs suppression of responses to noxious stimulation? Also noteworthy is the observation that the [ALF] required for maximum reduction of EMAC is not unlike that required for maintenance of satisfactory N_2O anesthesia in human patients.[2] In fact, it has not been possible to use Alf alone to maintain satisfactory anesthetic conditions in human surgical patients even with much higher [ALF].[4] Hence, it seems that the dog and human are similar in exhibiting a ceiling effect of [ALF] which is inadequate for general anesthesia in the absence of supplemental drugs.

References

1. Murphy MR and Hug CC Jr: The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. Anesthesiology 1982;57:485-488.
2. Ausems ME and Hug CC Jr: Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for lower abdominal surgery. Br J Anaesth 1983;55:191s-197s
3. Scott JC, Ponganis KV, and Stanski DR: EEG quantitation of narcotic effect: The comparative pharmacodymanics of fentanyl and alfentanil. Anesthesiology 1985;62·234-241.
4. Hall RI, Angert KC, Reeder DA, et al. Is alfentanil a complete anesthetic in humans? Abst. (Submitted for publication).

Table. Plasma concentration of alfentanil [ALF] and degree of enflurane MAC reduction resulting from incremental infusion rates. (Values are Mean ± SEM)

Inf rate\$	N	[ALF] (ng/ml)	EMAC\$\$	EMAC reduction (%)
Control	10	0	2.46 ± 0.10	0
0.625	4	17 ± 3	1.93 ± 0.26	24 ± 5*
1.6	9	42 ± 2	1.15 ± 0.15	53 ± 6*,**
8.0	7	223 ± 13	0.77 ± 0.14	69 ± 6*
32.0	9	1150 ± 142	0.74 ± 0.10	70 ± 3*,***
80.0	9	3035 ± 338	0.74 ± 0.08	70 ± 2*,***

\$ Infusion rate ug.kg^{-1}. min^{-1}
\$\$ EMAC = enfluirance vol % in end-tidal gas
*p< 0.05 vs control
**p<0.05 vs 0.625 ug.kg^{-1}min^{-1}
***p< 0.05 vs 1.6 ug.kg^{-1}.min^{-1}

Title: DOES AN EPIDURAL TEST DOSE PREVENT COMPLICATIONS OF EPIDURAL CATHETER INSERTION

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Introduction. The purpose of this study was to assess the incidence of complications related to epidural cathether insertion following two methods of local anesthetic administration.

Methods. The protocol was approved by the Human Experimentation Committee at the University of Toronto. Patients in whom there was a contraindication to epidural analgesia or the drugs used were excluded and informed consent was obtained. Patients were randomly assigned to one of two treatment groups. Group I ("wet") received 3 ml of 1.5% lidocaine with 15 ug of epinephrine through the needle prior to catheter insertion. Five minutes later a second identical dose was administered through the catheter. If there was no evidence of intravascular or intrathecal injection, 4 ml of 1.5% lidocaine without epinephrine was administered.
Patients in Group II ("dry") received no local anesthetic through the needle prior to insertion of the epidural catheter. After insertion, 3 ml of 1.5% lidocaine with 15 ug of epinephrine were injected as a test dose followed 5 minutes later by an additional 7 ml of 1.5% lidocaine without epinephrine. Maternal blood pressure and fetal heart rate were monitored for twenty minutes.

Prior to catheter insertion all patients received fluid preload of 750–1000 ml of balanced salt solution. A Portex "Blue Line" catheter was used. The loss of resistance technique, injecting no more than 2 ml of air was used to identify the epidural space.

Chi square and Student's t-test for unpaired data were used for statistical analysis. A p value of less than 0.05 was considered significant.

Results. One hundred and fifty patients were studied; 73 Group I and 77 in Group II. The patients were similar in age, gravidy, parity, and cervical dilatation.

The results are shown in the table.

	GROUP I	GROUP II	P VALUE
	n=73	n=77	
PARASTHESIA	23(31.5%)	38(49.3%)	$p<.05$
IV CANNULATION	6(8.2%)	8(10.3%)	ns
CATHETER REIN- SERTIONS	7(9.5%)	11(14.3%)	ns
MORE LOCAL	11(15.0%)	9(11.6%)	ns
TIME TO ANALGESIA (MINUTES)	11.8+/-6.6	11.4+/-7.7	ns

ns = no significant difference between Group I

Discussion. The incidence of parasthesia on catheter insertion was found to be significantly lower following the "wet" method compared to the "dry". Ten ml of air also reduces the incidence of parasthesia (1). Possibly the mechanical act of injection through the needle decreases the incidence of parasthesia by physically moving nerve roots away from the needle. This study demonstrates that a very small volume of local anesthetic (3 ml or the volume recommended as a test dose) is capable of reducing the incidence of parasthesias. Local anesthetic is preferable to air; injection of air may increase the risk of air embolus (2). Although a transient parasthesia is not dangerous, it may be uncomfortable, especially for the unpremedicated, pregnant patient. In addition, involuntary movement of the lower limb may be sufficiently violent as to cause accidental dural puncture with the needle.

The incidence of intravascular cannulation was the same for both groups. Ten ml of local anesthesia through the needle may reduce the incidence of intravascular cannulations (2). However, this volume could result in total spinal, seizures or severe cardiac dysrhythmias if accidentally given intrathecally or intravenously (4). Large volumes of saline could be used but this may dilute the local anesthetic making it less effective in relieving labour pain

In summary, administration of a 3 ml epidural test dose of local anesthetic through the needle in patients receiving epidural analgesia reduces the incidence of parasthesia with catheter insertion. This technique is safe and may reduce patient discomfort during the procedure while providing effective and prompt pain relief.

References.

1. Philip BK. Effect of epidural air injection on catheter complications. Reg Anesthe 1985; 10: 21-3.
2. Naulty JS, Ostheimer GW, Datta S, et al. Incidence of venous air embolism during epidural catheter insertion. Anesthesiology 1982; 57: 410-2.
3. Verniquet AJW. Vessel puncture with epidural catheters: experience in obstetric patients. Anaesthesia 1980; 35: 660-2.
4. Kotelko DM, Shnider SM, Daily PA, et al. Bupivacaine-induced cardiac arrhythmias in sheep. Anesthesiology 1984; 60: 10-18.

Title: OXYMORPHONE FOR USE IN PATIENT CONTROLLED ANALGESIA - THE IDEAL PCA DRUG?

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Introduction. Although Patient Controlled Analgesia (PCA) has been reported to provide superior analgesia and great patient satisfaction when compared to intramuscular injection, a recent study, using morphine, failed to show a significant difference in quality of analgesia or dosage used when P.C.A. was compared to IM administration in patients following cesarean delivery (1).

Oxymorphone is a potent semi-synthetic narcotic analgesic, providing excellent analgesia with minimal histamine release. Its potential advantages over morphine include a rapid onset, lower incidence of histamine release, and less sedation. These properties suggest oxymorphone to be ideally suited for use in P.C.A. We therefore proposed a study to evaluate oxymorphone as a suitable narcotic for P.C.A. in patients following elective C-section. Our experience using oxymorphone in this setting is presented in 12 patients.

Methods. Following institutional approval, written informed consent was obtained from 12 patients undergoing elective cesarean delivery. Epidural anesthesia was provided for surgery using 2% lidocaine with epinephrine 1:200,000 to obtain a T4 sensory level. Following delivery, a narcotic analgesic base was administered using 1 mg of oxymorphone intravenously in four divided doses.

In the PAR and for the next 24 hours, patients were able to self-administer further incremental doses of oxymorphone using the Bard Harvard PCA infuser when additional analgesia was required. The dosage administered was 4 mcg/kg pregnant weight. We calculated this dosage regimen based on previous experience using morphine in this setting (6 mg morphine equivalent to 1 mg oxymorphone).

Patients were continuously observed during the study period. Pain scores and patient satisfaction scores were obtained at two hourly intervals for the first 12 hours following delivery, and four hourly thereafter. In addition, the observer noted respiratory rates, degree of sedation, presence of pruritis, nausea and vomiting, and the need for supplemental medication during the study period.

Results. A total of 12 patients (N=12) participated in the study. During the first 24 hours following delivery, patients received an average of 16 mg oxymorphone for analgesia (range 9-24.5 mg). The total dose ranged from 0.11-0.29 mg/kg with a mean dose of 0.21 mg/kg. The mean hourly dose was .009 mg/kg/hr with a range of 0.005 to 0.012 mg/kg/hr.

The Bard PCA pump records number of attempts at self-medication in addition to number of successful injections administered. Over 82% of the time patients received a drug bolus when an analgesic demand was made, suggesting that the dose selected was adequate and that the onset of pain relief was rapid, occurring within the lockout interval of eight minutes of drug administration.

Pain scores and patient satisfaction related to time are shown for the 24 hour study period. No patient complained of severe pain (pain score of 7-10) during the study period. Seventy-two percent of patients reported complete satisfaction with the quality of their analgesia.

Mild nausea, not requiring treatment, was observed in two patients, and a further two patients received compazine 10mg i.m. for nausea and/or vomiting. No patients reported nausea beyond eight hours following surgery.

Transient mild facial pruritis, not requiring treatment, was observed in four patients. Neither the presence of pruritis or nausea could be related to dosage of narcotic received.

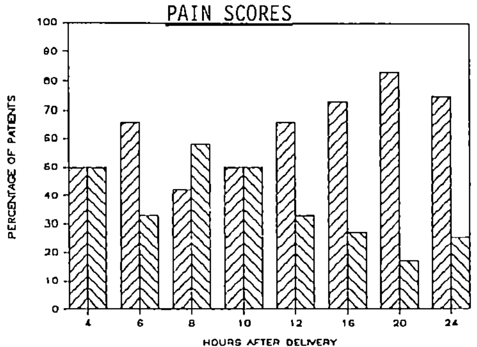
Discussion. Oxymorphone provided satisfactory analgesia with extremely rapid onset of action when administered using patient controlled analgesia in the post-cesarean section patient. Although the majority of patients reported mild pain, even those reporting moderate pain (viseolinear pain scores of 4-6) expressed complete satisfaction with their analgesia. It may be speculated that patients using patient controlled analgesia tolerate higher pain scores knowing that, if desired, they may obtain rapid relief of their pain.

The results of this prospective study show oxymorphone provides effective analgesia when used as patient controlled analgesia in the post-cesarean section patient. Further studies comparing oxymorphone to opioids currently used for patient controlled analgesia are warranted.

Reference.

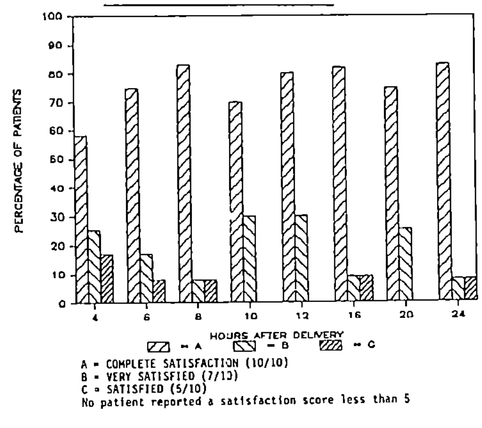
1. Harrison DM, Sinatra RS, et al.: Epidural and patient controlled analgesia for post-cesarean section pain relief. SOAP, 1986.

PAIN SCORES



No patient reported severe pain (7-10)

PATIENT SATISFACTION



A = COMPLETE SATISFACTION (10/10)
B = VERY SATISFIED (7/10)
C = SATISFIED (5/10)
No patient reported a satisfaction score less than 5

Title: AXILLARY BRACHIAL PLEXUS BLOCK: EFFECT OF COMPOUNDING BUPIVACAINE AND LIDOCAINE ON VENOUS LEVELS

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Introduction. Toxicity of local anesthetics is related to their plasma levels and several studies have been aimed at determining plasma concentrations of local anesthetics during various block procedures. Moore et al. (1) have studied bupivacaine during supraclavicular brachial plexus block and Vester-Anderson et al. (2) have compared blood levels of mepivacaine administered by either the interscalene or axillary approach. However, in an attempt to combine the beneficial characteristics of different drugs, mixtures of local anesthetics have been used (3). Raj et al. (4) monitored plasma levels of mixtures ('compounds') of local anesthetics, but since the constituent anesthetics were not studied singly, it is not possible to determine whether mixing drugs affected their uptake and/or elimination. We therefore determined to monitor the venous plasma levels of bupivacaine and lidocaine when these were administered as a mixture or singly using the same doses during brachial plexus blockade to ascertain whether compounding the drugs has any effect.

Methods. Fifteen ASA I or II patients scheduled for surgery of the hand, wrist or forearm, and who had consented to brachial plexus blockade by the axillary approach, were studied. Premedication was comprised of diazepam, 10 mg p.o., 1-1/2 hrs before anesthesia, and fentanyl, 0.1 mg IV immediately before starting the block procedure. The patients were divided into three groups: Group I - Mixture: These patients received 20 ml 0.75% bupivacaine and 20 ml 2% lidocaine containing 1:200,000 epinephrine. Group II - Bupivacaine: In this group, 40 ml 0.375% bupivacaine containing 1:200,000 epinephrine was given. Group III - Lidocaine: 40 ml 1% lidocaine was used.

A stop watch was started with the injection of local anesthetic and venous samples withdrawn at 5, 10, 15, 20, 25, 30, 40, 50, 60, 90 and 120 min. A paper record of the ECG was also made at these times. A close watch was kept for signs of a toxic reaction. The venous samples were analyzed for the relevant total and free local anesthetic. In addition, the alpha-1-glycoprotein concentration was also determined for each patient. The weight and sex of each patient was noted.

This study was approved by the Institutional Human Research Committee.

Results. There was no significant difference in the patients' weights between each group. Mixing the local anesthetics bupivacaine and lidocaine had no significant effect on the peak venous levels of either the free or total local anesthetic (Table 1). However, as is shown in Table 2, mixing the drugs influenced their uptake. There was a significant delay ($p < 0.05$) in reaching the peak total level for both lidocaine and bupivacaine when the drugs were mixed. In addition, the development of the peak level of free bupivacaine was also delayed.

TABLE 1

GROUP	PEAK PLASMA LEVEL (g/ml) TOTAL (+SE)	 FREE (+SE)
I (Lidocaine mixture)	1.58 ± 0.26	0.71 ± 0.12
III (Lidocaine only)	1.80 ± 0.40	0.82 ± 0.20
I (Bupivacaine mixture)	0.81 ± 0.14	0.06 ± 0.01
II (Bupivacaine only)	0.73 ± 0.20	0.06 ± 0.01

TABLE 2

GROUP	TOTAL (min + SEM)	FREE (min + SEM)
I (Lidocaine mixture)	78.0 ± 17.0	44.0 ± 8.0
III (Lidocaine only)	45.0 ± 12.6	44.0 ± 5.1
I (Bupivacaine mixture)	60.0 ± 16.0	42.0 ± 7.0
II (Bupivacaine only)	27.0 ± 8.0	11.5 ± 6.4

No cardiovascular or neurological complications were encountered in this study, and at no time did any signs of a toxic reaction occur.

Discussion. We have shown that 'compounding' bupivacaine and lidocaine delays onset of the peak level of the drugs but does not influence the plasma levels attained.

References

1. Moore DC, Mather LE, Bridenbaugh LD, Blafour RI, Lyons DF, Horton WG: Arterial and venous plasma levels of bupivacaine following peripheral nerve blocks. Anesth Analg 1976; 55:763-768.
2. Vester-Anderson T, Christiansen C, Hansen A, Sorensen M, Meisler C: Interscalene brachial plexus block: Area of analgesia, complications and blood concentrations of local anesthetics. Acta Anaesth Scand 1981; 25:81-84.
3. Bromage PR, Gertel M: Improved brachial plexus blockade with bupivacaine hydrochloride and carbonated lidocaine. Anesthesiology 1972; 36:479-487.
4. Raj PP, Rosenblatt R, Miller J, Katz RL, Carden E: Dynamics of local-anesthetic compounds in regional anesthesia. Anesth Analg 1977; 56:110-117.

Title: THE EFFECT OF FENTANYL ON VERAPAMIL PLASMA LEVELS AND HEMODYNAMICS IN DOGS

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Introduction. It has been previously established that during inhalational anesthesia, verapamil (V) produces a more pronounced myocardial depression[1,2] as a result of pharmacokinetic[3] and pharmacodynamic interactions. Because V may be indicated in patients with preoperative depressed cardiac function, it appears important that V myocardial depression is minimally effected by the presence of an anesthetic. We designed this study to assess the effects of fentanyl (F) on both the pharmacokinetics and pharmacodynamics of V.

Methods. Six dogs (20±2 kg) were chronically instrumented for measurement of mean aortic pressure (MAP), left ventricular (LV) dP/dt, heart rate (HR), PR interval, and coronary (Cor), carotid (Car), and renal (Ren) blood flows (BF). After recovering from surgery for at least 10 days, each dog received V (200 ug/kg IV over 10 min) awake and during F anesthesia (1.5 ug/kg/min for 6 hrs) on two different occasions, randomly assigned and separated by at least 4 days. After pancuronium injections (0.1 mg/kg IV), the dogs were intubated and ventilated mechanically. Hemodynamic function was continuously recorded. In addition, aortic blood samples for V determination were collected prior to and 1, 3, 5, 10, 15, 30, and 45 min and 1, 2, 3, 4, and 5 hr after V. Concentrations of V were analyzed by gas-liquid chromatography using nitrogen-phosphorous detection. Data were analyzed using an analysis of variance. When significant, paired t-tests were applied. Alpha was set up at a level of 0.05. Data are presented as mean ± SEM.

Results.

Pharmacokinetic: As indicated in Table I, F did not alter V pharmacokinetics.

Hemodynamic: V decreased LV dP/dt, and increased HR and PR interval in awake dogs. In the presence of F, the effects of V on HR and PR interval were similar while LV dP/dt remained essentially unchanged and a slight decrease in MAP was recorded (Table II).

Discussion. The hemodynamic and pharmacokinetic interactions between verapamil and high-dose fentanyl appear to be minimal. The present data are markedly different from those previously obtained in the presence of inhalational anesthetics. They suggest that high dose fentanyl is a more suitable anesthetic technique in patients with preoperative depressed myocardial function who may require intraoperative verapamil therapy.

TABLE I: Effects of F on V pharmacokinetics

		V	V + F
V_1	L	40 ± 4	36 ± 4
Intercompartmental Clearance	L/hr	211 ± 36	192 ± 44
Vdss	L	101 ± 17	100 ± 14
Total Clearance	L/hr	54 ± 6	64 ± 9
$B\text{-}t_{1/2}$	hr	1.64 ± 0.27	1.54 ± 0.15

Table II: Hemodynamic effects of F, V, and F + V (mean ± SEM)

	Control	V	F	V + F
MAP mmHg	94±6	94±6	117±6*	104±5†
HR bts/min	81±4	111±7*	72±4	91±6†
LV dP/dt mmHg/sec	3012±170	2693±208*	4206±420*	4068±384
PR sec	.12±.01	.15±.01*	.11±.01	.15±.01†
CarBF ml/min	125±13	126±10	127±15	140±21
RenBF ml/min	108±6	116±3	130±10	135±9
CorBF ml/min	36±4	41±5	37±10	71±29

* = $p < 0.05$ vs C; † = $p < 0.05$ vs F

References.

1. Chelly J, Rogers K, Hysing E, Taylor A, Hartley C, Merin R. Cardiovascular effects of and interactions between calcium blocking drugs and anesthetics in chronically instrumented dogs: I. Verapamil and halothane. Anesthesiology 1986; 64:560-567.
2. Rogers K, Hysing E, Merin RG, Taylor A, Hartley C, Chelly J. Cardiovascular effects of and interactions between calcium blocking drugs and anesthetics in chronically instrumented dogs: II. Verapamil, enflurane, and isoflurane. Anesthesiology 1986; 64:568-575.
3. Merin R, Chelly J, Abernethy D, Hysing ES, Jacobson L. Inhalational anesthetics alter the pharmacokinetics of verapamil. Anesthesiology 1985; 63:205(A).

TITLE:

ANESTHETIC IMPLICATIONS FOR MANAGEMENT OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION: A MATCHED COHORT STUDY OF CABG OPERATIONS

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INTRODUCTION: Emergency coronary artery bypass grafting (CABG) is being used for myocardial reperfusion and tissue salvage during acute myocardial infarction (AMI).[1] Although previous reports have demonstrated increased morbidity and mortality, no study has systematically compared the operative course of patients having an AMI with patients having elective surgery. In an effort to identify the anesthetic problems associated with these patients a retrospective chart review was made comparing patients undergoing emergency CABG during AMI with a carefully matched cohort group of patients having elective CABG.

METHODS: Twenty-three patients who had emergency CABG during AMI over an 18 month period were identified. Each patient had the onset of persistent chest pain within 12 hours of induction of anesthesia and S-T segment elevation of at least 0.2 mV on 2 or more ECG leads. The 23 AMI patients were matched by a computerized program for gender, surgeon, preoperative ejection fraction and aortic cross clamp time with 23 patients who had elective CABG contemporaneously. Patient characteristics, drug therapy, activated clotting times, blood administration, cardiac output, postoperative bleeding and complications were compared between groups. Results are shown as mean ± standard deviation. Statistical significance was determined with one-way analysis of variance or Chi square tests where appropriate.

RESULTS: The 23 AMI patients were anesthetized 5.9 ± 3.0 (range 1.5-11.0) hours after the onset of chest pain. Eighteen had anterior S-T elevation and five had inferior S-T elevation on the preoperative ECG. Fifteen AMI patients had streptokinase therapy and seven had attempted percutaneous coronary angioplasty prior to surgery. Patient characteristics are shown in Table 1.

Table 1.	AMI	(N)	Elective	(N)	P
Age (yr)	62±9.8	(23)	57±11	(23)	NS
EF (%)	50±10	(21)	54±10	(23)	NS
LVEDP (mmHg)	21±7.1	(18)	18±7.6	(21)	NS
Aorta Clamp time (min)	39+23	(23)	43±16	(23)	NS
Bypass time (min)	103±46	(23)	103±29	(23)	NS
Grafts (No.)	2.9±1.6	(23)	2.7±0.9	(23)	NS

A balanced anesthetic technique was used in both groups, employing similar anesthetic drugs (fentanyl, pancuronium, diazepam, and enflurane or halothane). Inotropic drugs were required more frequently in the AMI group both before (3/23 vs 0/23; p<.05) and at termination of bypass (12/23 vs 3/23; p<.005). Antiarrhythmic drugs were also used more often in the AMI patients (16/23 vs 5/23; p<.005). The 15 patients who received streptokinase had greater bleeding than their paired cohorts as shown in Table 2.

Table 2.	AMI SK (N)	ELECTIVE COHORTS (N)	P
CT Drainage-first 12 hours (cc)	1290±610 (15)	842±470 (15)	.03
ACT before heparin (sec)	159±107 (15)	110±21 (15)	.09
ACT - after protamine (sec)	171±98 (15)	126±37 (15)	.10
Blood Transfused (units)	8.73±5.0 (15)	6.27±2.5 (15)	.10

Three AMI patients died postoperatively. There was no mortality in the elective group. Electrocardiograms one day after surgery revealed new Q waves in 15 and sustained S-T elevation in 3 AMI patients. Three AMI patients without ECG evidence of infarction had significant elevations of CK-MB isoenzymes. One elective patient had new Q waves. The number of patients requiring postoperative ventilation for greater than 24 hours (10/23 vs 1/23; p<.005) and prolonged ICU care for greater than two days (9/23 vs 3/23; p<.05) was higher in the AMI group.

DISCUSSION: Patients undergoing emergency CABG during AMI represent greater surgical and anesthetic risks than elective CABG patients. They have a higher incidence of myocardial dysfunction requiring inotropic support that is particularly evident following cardioplegic arrest during cardiopulmonary bypass. They have a greater need for antiarrhythmic therapy and prolonged postoperative intensive care. Those patients given thrombolytic therapy have increased bleeding.

REFERENCE

1) Phillips SJ, et al: Reperfusion protocol and results in 738 patients with evolving myocardial infarction. Ann Thorac Surg 41:119-125, 1936.

Title: COMPARISON OF CUTANEOUS AND IN VITRO HUMAN MAST CELL HISTAMINE RELEASE BY MUSCLE RELAXANTS

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Introduction:

We have previously used the human foreskin mast cell as a model of anesthetic agent induced histamine release. It is not known whether responses to anesthetic drugs in those infant mast cells are functionally similar to those of the adult. For this reason we compared histamine release in our mast cell model to histamine release in vivo in adult humans using a series of concentrations of three commonly used muscle relaxants (vecuronium, atracurium and d-tubocurare) by measuring the wheal size resulting from their intradermal introduction.

Methods: Research Committee approval was obtained for the in vivo studies. Freshly excised human foreskins were cut into 8 to 10 pieces, then sectioned into 200 um widths using a Sorvall TC-2 tissue sectioner. Each sectioned piece was incubated in buffer for 30 min. at 37°C to determine basal histamine release. The pieces were then incubated with buffer (pH 7.4) containing d-tubocurare, vecuronium and atracurium in concentrations ranging from 10^{-5}M to 10^{-3}M for 30 min. to determine drug-induced histamine release. Residual histamine was obtained by boiling and homogenizing each piece. Histamine concentrations were analyzed by automated fluorometry. Basal histamine release and muscle relaxant-induced release were calculated as a percentage of total tissue histamine. For the in vivo studies, healthy adult subjects, taking no medications, were tested with histamine (positive control), saline (negative control), and three concentrations, 10^{-5}M, 10^{-4}M and 10^{-3}M, of each muscle relaxant. A drop of the solution was placed on the skin and a 27 gauge needle used to enter the skin to the depth of the bevel and pulled perpendicular to the skin to tent the skin and allow the test sample to enter the epidermis. After twenty minutes the resulting wheal size was measured. Data were analyzed using a one way analysis of variance, and regression analysis with $P<.05$ level of significance.

Results: In vitro testing revealed dose-related histamine release with d-tubocurare and atracurium. Vecuronium did not release appreciable amounts of histamine at any concentration. In vivo skin testing showed dose-related histamine release, as measured by wheal size, for both d-tubocurare and atracurium, but not for the vecuronium. Histamine release in vivo correlated well with histamine in vitro ($r=0.9$) (fig 1).

Discussion: Histamine release from the human foreskin mast cell preparation by d-tubocurare, atracurium and vecuronium does indeed correlate with that measured by wheal size in the adult skin. We therefore conclude that the infant foreskin mast cell model is a valid predictor of histamine release by muscle relaxants in vivo and can provide valuable information about mechanisms of histamine release by these and perhaps other drugs used in anesthetic practice.

Supported by NIH Grant 25831.

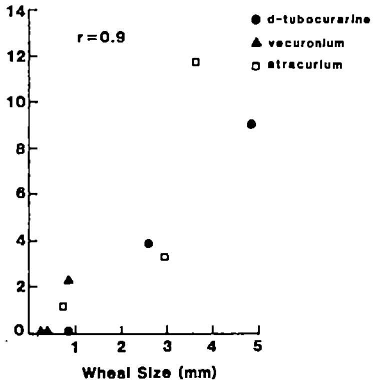

Figure 1 - Plot of percent histamine release against skin wheal size by d-tubocurare, vecuronium and atracurium 10^{-5}M, 10^{-4}M and 10^{-3}M.

Title: URINE OUTPUT AFFECTS URINARY CATHETER TEMPERATURE DURING RAPID WARMING

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Introduction: Urinary catheter temperature (UCT), an index of core temperature(1), is cleaner and less less invasive than rectal temperature (RT). Although differences among the various measures of "core" temperature are common(1,2), it is postulated that UCT reflects blood temperature because urine is a filtrate of blood(1). This study compared UCT with RT and esophageal (ET) and pulmonary artery (PAT) temperatures during and after rapid rewarming on cardiopulmonary bypass (CPB), emphasizing the influence of urine output on the agreement of UCT with ET, RT, and PAT.

Methods: With institutional approval and after informed consent from 24 adults to undergo cardiac surgery with CPB, disposable thermocouple probes were placed in the distal esophagus, rectum, and urinary bladder; a thermistor-tipped catheter was placed in the pulmonary artery. Thermocouple monitors with precision 0.1°C (Mon-A-Therm model 6500) were self-calibrated before each use. Auscultation verified proper esophageal probe placement(3). Urine output was measured in a Travenol urimeter. Beginning with the start of warming on CPB, temperatures and interval urine output were recorded every 10 min for two hours or until the termination of surgery. Mean temperatures at each time were compared using the Neuman-Kuels test. For each measurement, the pairwise differences UCT-ET, UCT-RT, and UCT-PAT were calculated. Each of these 3 temperature differences was related to urine output by correlation coefficient and least squares linear regression. Data during warming (N=81) and after CPB (N=193) were analyzed separately.

Results: Figure 1 shows the mean temperatures for all patients. At 10, 20, 30, and 40 min after the start of rewarming, ET behaved like PAT and UCT behaved like RT [(ET=PAT) > (RT=UCT) by Neuman-Kuels]. Total warming time was 37±10 (SD) min. Urine output was 26±21 ml per 10 min during rewarming and 52±44 ml per 10 min post-CPB. The table shows for each variable the slope, intercept, and correlation coefficient r, during warming. P-values refer to the likelihood that the slope is zero. Figure 2 is the scatter plot for ΔT=UCT-ET. During warming, urine output significantly contributes to the UCT-ET and UCT-PAT differences, accounting for about 18 and 12 percent of the variance respectively. Urine output did not influence the UCT-RT difference. Post-CPB, urine output did correlate with each of the three temperature differences. However, temperature differences (≥0.4°C) and regression line slopes (≤.0045) were too small to be of clinical significance.

TABLE: Correlation of ΔT with urine output

ΔT	N	Slopes*	Intercept*	r	P
UCT-ET	81	.042	-5.45	0.43	.0001
UCT-RT	81	.016	-1.09	0.18	.10(NS)
UCT-PAT	78	.043	-5.38	0.35	.0018

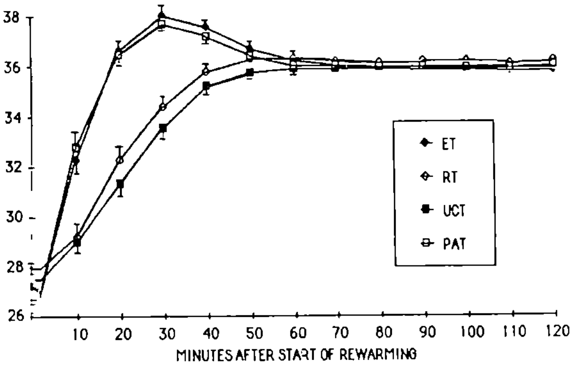
*ΔT = Slope • Urine Output (ml/10 min) + Intercept

Discussion: These data allow two conclusions. First, UCT is a good substitute for RT. UCT and RT measurements are indistinguishable during both relative thermal stability and rapid warming. Second, UCT is influenced by urine output: UCT approximates core temperatures better during abundant diuresis. These data favor the hypothesis that UCT measures core temperature during relative thermal stability(3). During rapid rewarming, however, UCT, like RT, lags behind the core measures ET and PAT, unless urine output is abundant (≈750 ml/hr). The small correlation coefficients (≤0.43) for ΔT vs. urine output are expected, since factors other than urine output (such as adiposity and blood flow distribution) contribute to the UCT-ET or UCT-PAT differences.

References:

1. Lilly JK, Boland JP, Zekan S: Urinary bladder temperature monitoring. Crit Care Med 1980; 8: 712-4.
2. Moorthy SS, Winn BA, Jallard MS, Edwards K, Smith ND: Monitoring urinary bladder temperature. Heart & Lung 1985; 14:90-3.
3. Cork RC, Vaughan RW, Humphrey LS: Precision and accuracy of intraoperative temperature monitoring. Anesth Analg 1983; 62:211-4.

FIGURE 1. Mean ± SEM Temperatures (connecting lines for visual ease)



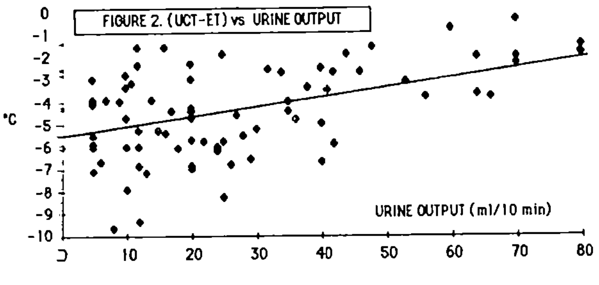


FIGURE 2. (UCT-ET) vs URINE OUTPUT

TITLE: PRIOR CAROTID SURGERY DOES NOT AFFECT ABILITY TO LOCATE THE INTERNAL JUGULAR VEIN

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INTRODUCTION: Prior carotid endarterectomy (CEA) is considered by many to be a contraindication to internal jugular vein (IJV) cannulation (1-2), presumably due to alteration of the relation of the IJV to surface landmarks. We employed ultrasonography to investigate the reliability of landmarks for IJV cannulation at both surgical sites (SS) and nonsurgical sites (NSS) in subjects with prior CEA.

METHODS: This study was approved by our institutional review board. Twenty-one subjects gave informed consent. Two commonly used techniques for IJV cannulation were selected: one represents an apical approach (3), the other an anterior approach (4). Each subject lay supine without head down tilt. For each technique on both the left and right sides, the ultrasound transducer was placed on the neck and directed like a needle according to the directions for the technique. One investigator viewed the image and identified and labelled arterial and venous structures according to their anatomic orientations and pulsation patterns. A photograph of the real-time image was obtained during normal respirations.

Each ultrasonographic image provided the following data: the intersection of the axis of the transducer with the image of the IJV, scored as yes ("hit") or no ("miss"); similiar scoring for the intersection of the axis of the transducer with the image of the CA; the distance along a needle's path from the skin to the center of the IJV image; and the angle between the IJV and the CA, measured by placing the origin of a protractor on the center of the IJV image using 0° as medial and $+90^\circ$ as anterior. Frequency data were analyzed by Chi-square contingency tables. Continuous variables were analyzed by paired or unpaired Student's t tests. Significance was defined as $P < 0.05$.

RESULTS: The 13 men and 8 women studied were aged between 54 and 85 years (mean 68). Between 6 months and 10 years had elapsed from CEA to this study (mean 3 years). Four subjects had had surgery on the right, 8 on the left, and 9 on both sides. The IJV was visualized in every view; the carotid artery (CA) was seen in 69 of 83 views. The table displays the hit frequency data for the two techniques. There were no statistical differences between the SS and NSS hit frequencies for either technique for either the IJV or the CA. The distance from the skin to the center of the IJV was $2.15 \pm .53$ cm (mean ± SD). Distance form skin to IJV did not vary with technique or from SS to NSS. The angle between the CA and the IJV was $-9 \pm 24^\circ$ (N=49) on the SS and $-14 \pm 16^\circ$ (N=20) on the NSS (P=NS, unpaired t test). In no photograph did the IJV lay medial to the CA.

DISCUSSION: Anesthesia texts state that prior CEA is a contraindication to IJV cannulation at that site (1-2). Though these recommendations are unreferenced, it is presumed that fibrosis, adhesions, or other surgical factors render surface landmarks unreliable as guides to location of the deeper structures, including the IJV.

This study shows that use of the sternocleidomastoid muscle (apical technique) or the carotid pulsation (anterior technique) as a landmark for cannulation in patients with prior CEA is associated with neither decreased chances of hitting the IJV nor increased chances of hitting the CA. Additionally, no difference was demonstrated between apical and anterior techniques, both at SS and NSS. This latter result agrees with a previous ultrasonographic investigation in which 15 different techniques were all equivalent with regard to IJV localization (5).

In young healthy volunteers (5), the IJV was found lateral and anterior to the CA (angle $-21 \pm 21^\circ$). The current data ($-14 \pm 16^\circ$) substantiate this relationship in elderly subjects. Furthermore, this relationship was not altered by CEA, the IJV remaining slightly anterior to the CA in most cases, and lateral to the CA in all cases.

Factors other than localization of the IJV and CA were not addressed in this investigation. For example, some clinicians choose to avoid neck manipulation in every patient with carotid artery disease, irrespective of prior surgery at that site. Also, prior CEA may produce adhesions or other tissue alterations (not quantified in this study) which could render difficult the actual passage of a needle and catheter.

These data suggest that localization of the IJV and risk of CA puncture are not altered by prior CEA. When central venous access is advantageous, cannulation of the IJV at the site of a prior CEA may be justified.

TABLE. Hit frequency data.

	Apical-SS	Apical-NSS	Anterior-SS	Anterior-NSS
IJV HIT	24	9	23	8
IJV MISS	6	3	6	4
%IJV HIT	80%	75%	79%	67%
CA HIT	3	3	2	2
CA MISS	24	7	20	8
%CA HIT	11%	30%	9%	20%
CA NONVIZ	3	2	7	2

Entries are number of patients.

REFERENCES:

1. Lake CL. Cardiovascular Anesthesia. New York: Springer-Verlag, 1985:58.
2. Hug CC. Monitoring. In Miller RD, ed. Anesthesia. New York: Churchill Livingstone, 1986: 439.
3. Daily PO, Griepp RB, Shumway NE. Percutaneous internal jugular vein cannulation. Arch Surg 1970; 101: 534-6.
4. Oda M, Fukushima Y, Hirota T, Tanaka A, Aono M, Sato T. The para-carotid approach for internal jugular vein catheterization. Anaesthesia 1981; 36: 896-900.
5. Metz S, Horrow JC, Balcar I. A controlled comparison of techniques for locating the internal jugular vein using ultrasonography. Anesth Analg 1984; 63: 673-9.

Title: BRAINSTEM AUDITORY EVOKED POTENTIALS DURING BALANCED ANESTHESIA WITH A SUFENTANIL INFUSION

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Introduction. Monitoring brainstem auditory evoked responses (BAER) is common for operations on the posterior fossa especially near the cerebellopontine angle[1]. BAER can be used for tumors, aneurysms, and microvascular decompressions, in addition to non-operative evaluation of head injuries and developmental abnormalities in the intensive care units.

Narcotic based anesthesia is recommended when recording intraoperative BAER because of minimal effects on the response.[1] Samra, et al[2] have shown that fentanyl does not significantly alter BAER. We recently reported[3] that a continuous infusion of sufentanil is suitable for neurosurgical cases and provides stable anesthesia as long as needed with the patient awake at the end of the procedure. We have now evaluated the effect of this anesthetic regimen on BAER.

Methods. The local institutional review board approved this study, and six patients gave informed consent. These patients underwent a variety of surgical procedures: Nashold's dorsal root entry zone (DREZ) procedure (2 patients), transphenoidal hypophysectomy (3 patients), lumbar laminectomy (1 patient), and cervical laminectomy (1 patient).

Baseline BAER's were done at least one day prior to the anesthetic. In addition to standard monitoring, the radial artery was cannulated for blood pressure and blood gas sampling. Inspired/expired gases were measured with mass spectrometry. Sufentanil 1 mcg/Kg was given prior to a thiopental induction (3-5 mg/Kg) and tracheal intubation facilitated with succinylcholine. A continuous infusion of sufentanil was begun at 0.6 mcg/Kg/hr for approximately the first hour, and the balanced anesthetic regimen was completed with 70% nitrous oxide and a non-depolarizing muscle relaxant. Sufentanil was titrated to maintain blood pressure and heart rate within 20% of baseline and usually ranged 0.26-0.29 mcg/Kg/hr after the initial incision and bone work. If vital signs were not controllable with additional sufentanil, isoflurane $\leq$ 0.3% end tidal and then a vasodilator was administered.

A Nicolet Pathfinder II recorded BAER. Needle electrodes were placed at the vertex and referenced to mastoids, maintaining impedance $\leq$5kOhms. Ground electrodes were placed on the shoulders. Stimulation was with clicks 20% greater than threshold hearing at a rate of 11.1Hz with contralateral masking. Bilateral recordings were done in all patients to aid correct identification of all peaks. 2000 artifact free repetitions were obtained for a complete recording. Recordings were done every hour until the end of the infusion.

Results. Excellent operating conditions and hemodynamic stability were provided by the anesthetic regimen with all patients awake at the end of the procedure.

Three peaks (I, III, V) were subjected to statistical analysis at baseline, 1 hour after induction, and end of infusion. (Table I) The right minus left latencies varied 0-0.3 msec, so latencies were averaged. As shown in the Table, there was no significant difference between the latencies observed prior to anesthesia, after 1 hour of anesthesia, and before the end of the infusion, as measured by ANOVA (2 way analysis of repeated measures) and Duncans new multiple range test.

Discussion. A sufentanil based balanced anesthetic technique provides excellent operating conditions, and hemodynamic stability with rapid awakening at the end of the procedure. We were not able to demonstrate a significant change in BAER throughout a balanced anesthetic with a sufentanil infusion.

TABLE 1:	Baseline	1 hour	Closing
I*	2.46±.172	2.51±.215	2.63±.165
III	4.72±.23	4.88±.175	4.96±.151
V	6.73±.198	6.71±.322	6.81±.249

*All values are mean±SEM (msec).

References.

1. Grundy BL: Intraoperative monitoring of sensory-evoked potentials. Anesthesiology 1983; 58:72-87.

2. Samra S, Lilly DJ, Rush NL, Kirsh MM: Fentanyl anesthesia and human brain stem auditory evoked potentials. Anesthesiology 1984; 61:261-265.

3. Hyman SA, Berman ML, Bullington JC, Flanagan JFK, Langford MD. The continuous infusion of sufentanil during neurosurgical procedures. (Submitted for publication.)

TITLE: **INTRATHECAL MORPHINE'S EFFECT ON THE POSTOPERATIVE COURSE OF PATIENTS UNDERGOING ABDOMINAL AORTIC SURGERY**

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Introduction: Patients undergoing abdominal aortic surgery have a recognized incidence of significant perioperative complications including respiratory failure, myocardial infarction, and renal failure.^{1,2} This retrospective study was undertaken to determine the effect of a single dose of intrathecal morphine on the postoperative course of patients undergoing abdominal aortic surgery.

Methods: Following institutional approval, the hospital records of all patients (N=75) undergoing elective abdominal aortic surgery at our hospital between May, 1985 and June, 1986 were reviewed. Patients were divided into two groups based upon whether they had received intrathecal morphine (ITM Group) or had not received it (Control Group). All patients were monitored with a V_5 ECG, an intraarterial catheter and either a central venous or pulmonary artery catheter. General anesthetic technique and whether or not a patient received ITM were at the discretion of the staff anesthesiologist. The occurrence of intraoperative or postoperative pulmonary edema, myocardial infarction, renal failure and death were obtained from data in the chart. Statistical comparisons of time to extubation, ICU stay, length of postoperative hospital stay and cost of hospitalization in the 2 groups were made using Student's T-test.

Results: Thirty-nine patients received ITM (0.5-1.0 mg) while 36 were in the control group. Pulmonary artery catheters were placed in 30/39 (77%) of the ITM patients and in 30/36 (83%) of the control group. There were no differences between the ITM and the control group in mean age (66±9 vs 63±8 yrs), duration of the surgical procedure (3.1±1.0 vs 3.6±1.2 hrs) or intraoperative blood loss (1200±800 vs 1300±800 ml). There were no significant intraoperative or ITM-related complications. There were no postoperative deaths in either group. One patient in each group had a myocardial infarction postoperatively.

The significant differences between the 2 groups are listed in the Table. Four (4) patients in the control group had clinically significant pulmonary edema, compared to only one patient who received ITM. Control patients had a longer time from the end of surgery until extubation, a longer postoperative ICU stay, a longer postoperative hospitalization time, and greater total cost of hospitalization.

Discussion: This retrospective study suggests that patients having elective aortic surgery who receive ITM have a shorter and less expensive postoperative hospital stay and a lower incidence of pulmonary edema than do patients not treated with ITM. The usual postoperative respiratory changes of atelectasis and decreased vital capacity may have been prevented by ITM, resulting in shorter ICU and hospital stays. Postoperative pain often produces systemic hypertension which may result in left ventricular failure in this group of patients who are likely to have coronary artery disease. By reducing postoperative pain, ITM also may be expected to decrease the frequency of left ventricular failure and pulmonary edema.

Conclusion: This retrospective study suggests that the postoperative courses of patients undergoing abdominal aortic surgery are improved when ITM is administered immediately prior to surgery. The simple and relatively safe technique might result in a significant cost savings to the patient, and should be given more widespread consideration and investigation.

TABLE (ALL RESULTS MEAN ± SD)

	CONTROL (N=36)	ITM (N-39)
TIME TO EXTUBATION (HRS)	10.3 ± 10.2	3.5 ± 6.6*
ICU STAY (DAYS)	3.3 ± 1.9	2.4 ± 1.1*
POSTOP STAY (DAYS)	10.7 ± 4.0	8.7 ± 2.0*
COST OF HOSPITALIZATION($)	16666 ± 6283	13796 ± 3386*

* $P < 0.05$ ITM VS CONTROL

References

1. Young AE, Sandburg GW, Couch NP: The reduction of mortality of Abdominal Aortic Aneurysm resection. AM J Surg 134:585-590, 1977.
2. Steen PA, Tinker JH, Tarhan S: Myocardial reinfarction after anesthesia and surgery. JAMA 239:2566-2570, 1978.

Title: THE HEMODYNAMIC AND OXYGEN TRANSPORT RESPONSES TO AUTOMATED ACUTE NORMOVOLEMIC HEMODILUTION

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Introduction: An alternative, risk-limiting procedure to homologous blood transfusion is autologous blood transfusion. Currently, three techniques are available: predonation, intraoperative salvage and intraoperative acute normovolemic hemodilution. Hemodilution offers the greatest advantages, particularly when combined with predonation. The major advantages of hemodilution include optimization of organ blood flow, reduction of myocardial work, the administration of functional platelets and coagulation factors, and possible reduction of surgical blood loss. We have previously demonstrated that automation of the hemodilution process improves the safety and accuracy of hemodilution, reduces blood loss, reduces or eliminates homologous blood and component transfusion, and shortens the duration of surgery [1]. The aim of this study was to examine the effects of acute normovolemic hemodilution on hemodynamic variables and oxygen transport during spinal fusion.

Methods: "Automated" acute normovolemic hemodilution (AANHD) was performed on seven consecutive patients ($\bar{x} \pm$ SEM, age 15.3 ± 5.4 years, body weight 53 kg ± 21.58 kg) undergoing spinal fusion with instrumentation for idiopathic or non-neural scoliosis Institutional approval and individual informed consent was obtained. Following induction of high-dose fentanyl anesthesia with isoflurane and institution of mechanical ventilation, an arterial line and thermodilution pulmonary artery catheter were inserted. After placement in the prone position, AANHD to a target hematocrit of 20% or 22% was acheived in a manner as previously reported using an IBM-Cobe 2997 cell separator [1]. The harvested ACD-A anticoagulated blood was stored at room temperature and returned to the patient prior to the termination of surgery. Normothermia was maintained throughout surgery. Cardiopulmonary and hematologic variables were measured. Nonparametric and parametric inferential analyses were performed on all data.

Results: The raw and derived results will be presented in two categories: 1) AANHD protocol variables and 2) hemodynamic and oxygen transport responses to AANHD, surgery and reinfusion of the autologous product. In 3 patients there were 2-4 units of predonated autologous blood reinfused during surgery. In general, as compared to our previous studies, the hemodynamic variables (HR, CVP, MAP, CO, and SVR) exhibited similar increasing or decreasing trends immediately following AANHD when compared to postinduction values. There were two significant changes, namely, a transient increase in CVP and a decrease in SVR. However, at the second, third and fourth intraoperative hourly measurements, there were significant decreases in CO and MAP, and an increase in SVR. With respect to the oxygen dynamic changes, significant decreases were observed in oxygen delivery and consumption one hour following AANHD and lasting throughout surgery. During the 2-4 hour, post AANHD period, a significant increase in oxygen extraction occurred. No significant changes were observed in the $a\bar{v}O_2$, $P\bar{v}O_2$ and $S\bar{v}O_2$.

Discussion. Our data indicate that the "automated" protocol with moderate ANHD was accurate and the immediate hemodynamic changes were minor. The subsequent intraoperative hemodynamic and oxygen dynamic changes, which included increased oxygen extraction, were complex and multifactorial, and were immediately reversed by reinfusion and awakening.

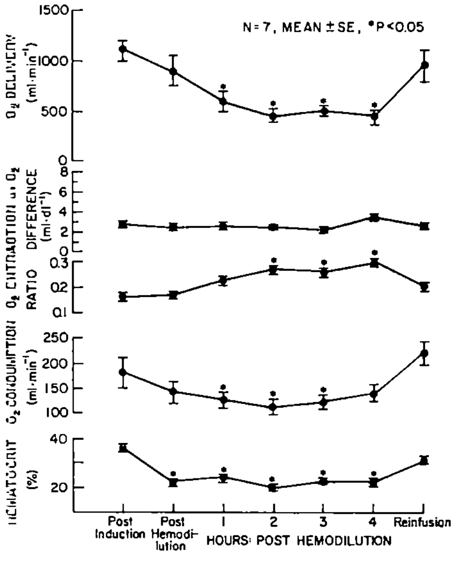
References.

1. Kafer ER, Isley MR, Hansen T, et al. Automated acute normovolemic hemodilution reduces blood transfusion requirements for spinal fusion. Anesth. Analg. 65:S1-S76, 1986.

Table and **Figure 1.** Hemodynamic and oxygen transport variables.

Variable	Post Induction	Post AANHD	Intraop. Hr 1	2	3	4	Reinfusion (ICU)
HR (beats min)	83 ±10	79 ±10	84 ±8	78 ±6	86 ±10	88 ±6	89 ±5
CVP (mm Hg	6 ±2	12* ±3	8 ±2	7 ±2	6 ±2	8 ±2	5 ±1
MAP (mm Hg	76 ±3	82 ±5	74 ±5	64* ±3	67* ±4	74 ±7	91 ±6
SVR (dyne/ cm-5)	1063 116	685* ±137	870* ±98	1329* ±191	1215* ±147	1358* ±200	1407 ±205
CO (L/min	6.34 ±0.66	7.31 ±1.12	4.73 ±0.69	4.11* ±0.64	4.20* ±0.62	3.76* ±0.55	6.43 ±0.83

Statistical significance of difference from post induction *p <0.05; n=7, MEAN, ± SEM.



Title: EFFECT OF ESMOLOL ON LEFT VENTRICULAR FUNCTION IN THE AWAKE DOG

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Introduction. Esmolol (E) is a fast acting water soluble beta-1-adrenergic receptor antagonist. An analysis[1] of data from 369 patients treated with E has suggested that there is a decrease in the benefit-risk (systolic hypotension) ratio for E dosages greater than 100 mcg/kg/min. Since E does not decrease systemic vascular resistance, E-induced hypotension must be due to decreased cardiac rate and contractility. The present investigation was designed to examine the effects of E on left ventricular (LV) function in the awake dog, a preparation with little chronotropic sympathetic tone, thereby isolating the inotropic effects of E.

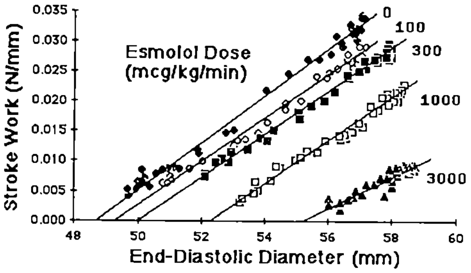
Methods. Nine dogs chronically instumented under general anesthesia with ultrasonic dimension transducers oriented across the LV minor axis diameter, pneumatic occluders positioned around both venae cavae, a silicone rubber tube secured in the base of the left atrial appendage, and a tube with multiple side holes positioned in the pleural space were studied in an awake unmedicated state. LV transmural pressure (LVTMP) and minor axis diameter (D) were measured by micromanometers and sonomicrometry, respectiveley. Vena caval occlusions (VCO) were performed to obtain stroke work (SW) (area within LVTMP-D loop) over a range of preloads during E infusions of 0 (control), 100, 300, 1000, and 3000 mcg/kg/min (n=9), at 15 and 30 min after termination of E (n=8), and 10 min after a 1 mg/kg bolus of propranolol (P) (n=6). The linear relationship between SW and end-diastolic D (EDD) was characterized for each VCO by a slope (M) and x-intercept (xint). Preload recruitable stroke work (PRSW) was used to assess LV function and was calculated[2] for each VCO as M/2 times the square of the difference between EDDMAX and xint, where EDDMAX was the largest EDD observed in a particular dog. HR, mean LV ejection pressure (MEP), and LV dP/dt were determined as mean values from the 10 cardiac cycles prior to each VCO. Data were compared vs. control by Student's 2-tailed paired t test.

Results. There were no statistically significant changes in M, but xint increased ($p<.05$) at 300 and 3000 mcg/kg/min (Figure). HR was different from control only at the highest E dose. DP/dt, MEP, and PRSW were depressed from control at E doses ≥300 mcg/kg/min. All parameters except dP/dt recovered within 30 min following termination of E. Only dP/dt was different ($p<.05$) from control following P (Table).

Discussion. In the awake dog, moderate to large doses of E depress LV function independent of changes in HR. Although arterial pressure was not measured, this study suggests that hypotension seen with E could be largely due to depressed contractile function. The SW-EDD relation has been shown to be a sensitive index of ventricular function that is relatively independent of preload and physiologic changes in afterload[3]. PRSW incorporates both this relation and relative changes in xint. PRSW values reported here indicate moderate to severe depression of LV performance during E above 100 mcg/kg/min. The increases in xint suggest diastolic dysfunction as a major component of this depression, which may partially explain increases in pulmonary capillary wedge pressure seen in some clinical studies[4] with E. Increased HR at the highest E dose might reflect beta-1 blockade at the sinoatrial node plus vagal withdrawl due to baroreceptor activation. The lack of HR effect by either E or P and the lack of inotropic effect by P suggest that the negative inotropic effect of E in this model is not wholly by beta-1 blockade. E produces predictable decrements in contractility, which should lower myocardial oxygen requirements; applied judiciously, this could be a useful property for patients with ischemic heart disease.

References.

1. Sung RJ, Blanski L, Kirshenbaum J, et al. Clinical experience with esmolol, a short-acting beta-adrenergic blocker in cardiac arrhythmias and myocardial ischemia. J Clin Pharmacol 1986; 26(suppl A):A15-A26.
2. Glower DD, Spratt JA, Tyson GS, Newton JR, Wolfe JA, Rankin JS. Quantification of regional myocardial function after acute ischemic injury (Abstract). J Am Coll Cardiol 1984;3:547.
3. Glower DD, Spratt JA, Snow ND, et al. Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. Circulation 1985;71:994-1009.
4. Newsome LR, Roth JV, Hug CC, Nagle D. Esmolol attenuates hemodynamic responses during fentanyl-pancuronium anesthesia for autocoronary bypass surgery. Anesth Analg 1986;65:451-456.



SW-EDD relation in one dog during vena caval occlusions.

Dose	0	100	300	1000	3000	15 min	30 min	P
PRSW	.242	.225	.188*	.188*	.079*	.174*	.193	.163
(N)	±.037	±.032	±.029	±.030	±.022	±.025	±.033	±.027
HR	91	90	92	94	128*	93	90	87
(bpm)	±5	±5	±6	±7	±4	±7	±7	±8
MEP	95	95	92	88*	82*	88	91	98
(mm Hg)	±4	±6	±5	±5	±5	±3	±4	±3
dP/dt	1842	1811	1591*	1568*	1051*	1506*	1594*	1617*
(mm Hg/sec)	±120	±121	±105	±116	±103	±23	±42	±44

mean±S.E.M., *$p<0.05$ vs. control

Title: INTRATHECAL DIAMORPHINE: EFFICACY, DURATION, OPTIMAL DOSE AND SIDE EFFECTS

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Introduction. Intrathecal opiates are reported to provide profound, prolonged analgesia through their binding to opioid receptors within the spinal cord. In order to ascertain the optimum dose of intrathecal diamorphine (diacetylmorphine, heroin) we used a range of doses in patients undergoing a uniform procedure (total knee replacement) which reliably induces severe postoperative discomfort. Diamorphine may have a real and unique advantage in behaving akin to a highly lipophilic drug within the cerebrospinal fluid (CSF), but like morphine in the spinal cord.[1]

Methods. Fifty patients scheduled for total knee replacement were included in this study after giving written informed consent and institutional approval was obtained. They all received subarachnoid anesthesia, bupivacaine 0.5% plain, 15mg, with or without additional diamorphine, 0.25mg, 0.75mg, 1.5mg, or 2.5mg mixed together with the local anesthetic. The subjects were randomly assigned to a treatment group and the drugs were administered in a double-blind manner. No premedication was given and systemic opiates were withheld until requested or deemed necessary in the postoperative period. Assessments commenced 2 hours after the subarachnoid injection and continued for 20 hours. These observations comprised an analysis of pain and/or analgesic effect using a visual analogue pain score (VAPS) and rank pain score system (RPS). Adverse effects such as excessive sedation, pinpoint pupils, reduction in respiratory rate, nausea, vomiting, pruritus and urine retention were sought. Supplementary postoperative morphine analgesia was initially administered intravenously as required and/or requested by the patient. Thereafter intramuscular morphine was given as deemed appropriate.

Results. Intrathecal diamorphine has the ability to delay the onset of severe postoperative pain and lengthen the interval between the initial perception of discomfort and the need for supplemental analgesia. It performs best with doses of 0.75mg or greater. The quality of analgesia observed was similar in all the groups. The amount (total milligrams) and number of doses of additional morphine did not differ significantly between any of the study groups. Pruritus was common in those receiving intrathecal opioid. The incidence of nausea and vomiting was high in all categories. Clinically significiant respiratory depression was not encountered. The results of the time to initial discomfort (T-Pain), time to supplemental systemic analgesia (T-Morphine), and side effects are shown in Tables 1a, 1b, and 2.

Discussion. Intradural diamorphine is safe and moderately effective. It has the capacity to provide impressive analgesia of extended duration in those subjects susceptible to its effect. Unfortunately it is, on occasions, incapable of providing satisfactory analgesia even in high dosage. Sufficient quantities of opioid necessary to ensure both spinal and supraspinal effects, may be required to provide the superior analgesia attributable to intradural opioid therapy. The spinal opioid receptor system has inherent limitations when confronted with the severe postoperative pain encountered following knee replacement surgery. Pruritus is the only adverse effect unique to this treatment.

References.
1. Moore A, Bullingham R, McQuay H, Allen M, Baldwin D, Cole A: Spinal fluid kinetics of morphine and heroin. Clin Pharmacol Ther 1984;35:40-45.

Table 1a. T-Pain
Diamorphine Dose(mg)

	Zero n=12	0.25mg n=7	0.75mg n=17	1.5mg n=7	2.5mg n=7
Median	5	6	5.5	5.5	6
Mean	4.7	5.57	6.1	5.86	6.14
SD	0.81	0.81	2.04	1.07	0.54
SEM	0.24	0.31	0.50	0.40	0.20
Range	3.5-6	4-6.25	4-13	5-8	5.5-7.25

Table 1b. T-Morphine

Median	5.25	6.75	7.5	8	7.75
Mean	5.3	7.43	8.2	12.7	14.0
SD	0.68	1.1	4.33	7.35	8.73
SEM	0.20	0.42	1.10	2.7	3.31
Range	4-6.75	4.25-10.75	5.5->24	5.75->24	6.5->24

Table 2. Adverse Effects
Diamorphine Dose (mg)

	Zero n=12	0.25 n=7	0.75 n=17	1.5 n=7	2.5 n=7
Pruritus	0	2	10	6	5
Nausea/Vomiting	6	3	11	5	7
Urinary Retention (requiring catheterization)	2	1	4	1	2
Respiratory Rate (<10 breaths/min)	1	0	0	0	0
Marked Sedation	1	0	1	0	2
Pinpoint Pupils	1	0	0	0	0

Title: INTRAPLEURAL ANESTHESIA FOR POST THORACOTOMY PAIN RELIEF

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Introduction. Reiestad et al recently reported intrapleural anesthesia as a new technique for the treatment of postoperative pain in patients who underwent cholecystectomy, renal surgery, and breast surgery (1). Intrapleural technique has several advantages when compared to alternative techniques in the treatment of postoperative pain. The purpose of the present study is: 1. to investigate the efficacy of intrapleural anesthesia in the management of postoperative pain in thoracotomy patients, and 2. to measure the plasma concentrations of bupivacaine following the intrapleural administration of 20 ml of 0.5% bupivacaine with and without epinephrine.

Method. Fourteen patients (ages 28-70) who underwent thoracotomy for various types of lung surgery including partial pneumonectomy, lung biopsy, and repair of injured thoracic aorta were included in this study. Six of these 14 patients were included for the measurement of plasma concentrations of bupivacaine following intrapleural administration. With the prior approval from our institutional review board, informed consent was obtained from each of the patients. At the end of the surgical procedure and before the closure of the thorax, an epidural catheter was placed in the pleural space by the surgeon under direct vision. The catheter was introduced through the nearest space adjacent to the incision site. The tip of the catheter was placed posteriorly in the pleural space and the catheter was secured with one or two skin sutures. All of the patients received 20 ml of 0.5% bupivacaine (7 patients with and 7 patients without epinephrine) in the recovery room as initial pain therapy. Patients also received subsequent doses of similar volume of either 0.25% or 0.5% bupivacaine up to 4 times a day for a maximum duration of 7 days. Blood samples were collected through an arterial line in 6 patients at the end of 5 min, 15 min, 30 min, 1 hr, 2 hr, 3 hr, and 5 hr following the intrapleural administration of initial dose of 20 ml of 0.5% bupivacaine (with epinephrine 2 patients, without epinephrine 4 patients). Plasma was immediately separated and refrigerated for the determination of bupivacaine concentrations by gas chromatography as described by Park et al (2).

Results. Results are summarized in tables 1 and 2. Moderate to excellent pain relief was achieved following intrapleural administration of bupivacaine in patients who underwent lateral and posterior thoractomies. No relief was achieved in 3 patients who underwent anterior thoracotomies. No pain relief was also achieved in one patient in whom the catheter tip was left anteriorly rather than posteriorly. The mean peak plasma concentratons of bupivacaine with and without epinephrine were 0.37 mcg/ml and 1.7 mcg/ml, respectively.

Discussion. Our preliminary study of intrapleural anesthesia as a modality of postoperative pain relief in 14 thoracotomy patients show that intrapleural anesthesia is effective in patients who undergo lateral and posterior thoracotomies and not effective in patients who undergo anterior thoracotomy. Our data also suggest that bupivacaine probably should be used with epinephrine as peak concentrations measured were less when bupivacaine was used with epinephrine. No apparent complications were noticed even when the catheter was left for a duration of one week.

References.

1 Reiestad F, Stromskag KE. Interplural catheter in the management of postoperative pain, a preliminary report. Regional Anesth 1986; 11:89-91

2 Park GB, Erdmansky PE, et al. Analysis of mepivacaine, bupivacaine, etidocaine, lidocaine and tetracaine. J Pharm Sci 1980; 69:603-605

Table 1

Patients n=14	Thoractomy Type	Pain Relief None	Pain Relief Good	Pain Relief Duration
3	Anterior	3	-	-
11	Lateral, Posterior	1*	10	4-8 hr

* Catheter left in anterior pleural space.

Table 2: Plasma Bupivacaine Concentrations (mcirograms/ml)

Patients	Time after injection (min) 5	15	30	60	120	180	300
1**	1.1	1.0	0.7	0.4	0.5	0.3	0.2
2**	3.5	3.6	2.7	1.0	0.6	0.2	0.2
3**	1.2	0.7	0.7	1.0	NM	0.5	0.2
4**	0.8	0.8	0.7	0.5	0.3	0.2	0.1
5*	0.1	0.2	0.2	0.2	0.3	0.1	0.0
6*	0.3	NM	0.3	0.3	0.4	0.3	0.2

* with epinephrine 1:200,000
** without epinephrine
NM = not measured

Supported by the Study Center for Anesthesia Toxicology, Vanderbilt.

Title: EFFECT OF PREECLAMPTIC PREGNANCY ON PLASMA PSEUDOCHOLINESTERASE ACTIVITY

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Introduction. Several investigators demonstrated that there is a decrease in plasma cholinesterase activity in normal pregnancy.[1] However, previous studies have provided conflicting data regarding plasma cholinesterase activity in preeclamptic pregnancy.[2] Hepatic dysfunction is known to cause a decrease in pseudocholinesterase activity. Preeclamptic pregnancy is associated with a significant hepatic dysfunction. Preeclamptic parturients receive magnesium which is known to prolong the duration of action of succinylcholine. It is of value for anesthesiologists to know the alterations of plasma cholinesterase activity associated with preeclampsia. Therefore, we studied plasma pseudocholinesterase activity in preeclamptic pregnancy at term.

Methods. With prior approval from our institutional human protection committee, we included 11 healthy non-pregnant women (ages 20-34), 11 normal pregnant women at term (ages 18-35), and 11 preeclamptic pregnant women at term (ages 18-40). A colorimetric method described by Ellman was used in the determination of plasma cholinesterase activity.[5] Six ml of heparinized blood was collected from each of the informed volunteer patients, plasma was separated and used for cholinesterase assay. The reaction system consisted of 3 ml of sodium phosphate buffer (0.1 mM, pH 8.0) containing 0.32 mM 5,5'-dithiobis-2-nitrobenzoic acid (DTNB) and 0.6 mM acetylthiocholine iodide. Dibucaine numbers were determined using a 0.1 mM concentration of the enzyme inhibitor in the final reaction medium. Readings were observed for 5 min at 410 nm in a Beckman Model 24 recording spectrophotometer at 24° C. Duplicate cholinesterase activities were measured for each patient plasma.

Data were analyzed for statistical significance by using a Student's t-test (two tailed p-value) with a Bonferroni correction for three test groups.

Results. The means and S. D. of plasma pseudocholinesterase activity of all the patients are shown in Table 1. There is a 41% decrease in cholinesterase activity in normal pregnant when compared to normal non-pregnant women. There is a 60% decrease in cholinesterase activity in preeclamptic pregnant when compared to normal non-pregnant women, and 32% decreae when compared to normal pregnant women. The dibucaine numbers (DN) of all the samples were found in the normal range (78-90).

Discussion. Plasma pseudocholinesterase is a mucoprotein produced in the liver which is responsible for most of the recovery from muscle paralysis produced by succinylcholine. Plasma cholinesterase is also responsible for the hydrolysis of ester type of local anesthetics including procaine, chloroprocaine and tetracaine.

Data from several investigators agree that cholinesterase activity declines during normal pregnancy. Tourtellotte reported in 1950 that there is a decrease in cholinesterase activity in preeclamptic pregnancy when compared to normal pregnancy. However, Pritchard in 1955 reported that there is no significant difference in cholinesterase activity between normal and preeclamptic pregnant patients. This disagreement could be due to the different techniques they used to measure plasma pseudocholinesterase activity.

The mechanism for a decrease in plasma cholinesterase activity in normal and preeclamptic pregnancies have not been elucidated. Various explanations including hemodilution, hepatic dysfunction, and hypoalbuminemia were offered as possible mechanisms for the decrease in plasma cholinesterase activity in pregnancy. Viby-Mogensen reported in 1980 that it is possible to predict duration of apnea and time of 100% twitch recovery following the administration of succinylcholine, utilizing correlation with plasma cholinesterase concentration.[6] Prolongation of apnea from succinylcholine was noted by investigators in the presence of low cholinesterase activity in normal pregnancy[1] and in the presence of therapeutic levels of magnesium in the plasma. We believe an additional explanation of the prolonged neuromuscular action of magnesium sulphate in preeclamptic pregnancy may be suggested by our data.

In conclusion, our data confirm that both normal and preeclamptic pregnancies are associated with a significant decrease in plasma pseudocholinesterase activity ($p<0.001$). Our data also suggest that there is a significant decrease in cholinesterase activity in preeclamptic pregnant when compared to normal pregnant women ($p<0.001$).

Table 1: Plasma Pseudochlinesterase Activity (mM per ml per minute)

Subjects	Mean	S.D.	p*
Normal non-pregnant	438	81	<0.001
Normal pregnant	257	25	<0.001
Preeclamptic pregnant	173	18	<0.001

*Two tailed p-values with Bonferroni's correction. (n=11 each group)

References.

1. Shnider SM: Serum cholinesterase activity during pregnancy, labor and the puerperium. Anesthesiology 1965; 26:335.
2. Pritchard JA: Plasma cholinesterase activity in normal pregnancy and in eclamptogenic toxemias. Am J Obstet-Gynec 1955; 70:1083.
3. Ellman GL, Courtney KD, Andres V, Jr., et al: A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem Pharmacol 1961; 7: 88-95.

Title: POSTOPERATIVE ARTERIAL OXYGEN SATURATION IN THE PEDIATRIC POPULATION DURING TRANSPORTATION

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Introduction. Hypoxemia in the Recovery Room (RR) is well documented both in the pediatric[1] and adult[2] population. However the pediatric population has not been studied for oxygen saturation (SaO_2) during transport from the operating room (OR) to RR. The purpose of this study was to monitor desaturation by pulse oximetry (Nellcor) in healthy pediatric patients during transport from the OR to RR.

Methods. Informed consent was obtained following the institutional guidelines on human experimentation. 60 ASA I and II patients between 1 month and 14 years were entered into the study. Patients were devided into 3 subgroups: Group I: 0-6 months n:10; Group II: 7-12 months n:10 and Group III: 13 months-14 years n:40. These patients underwent elective outpatient surgery of various duration. 48 patients were induced with O_2N_2O halothane, 9 were given rectal brevital and 3 were induced with IV Pentothal. Eight patients also received Atracurium which was reversed with atropine 0.02mg/kg and neostigmine 0.06 mg/kg. At the end of the procedure after extubation or at the end of mask anesthesia 100% O_2 was given for 3 minutes. The oxygen was then discontinued and the patients moved to the RR in the lateral position. SaO_2 was measured by securing the pulse oximetry sensor on the toe or finger of the patient during transport from OR to RR. Only one data point was collected for each patient which represents the lowest SaO_2 occuring during transport. Transportation lasted 120 - 180 seconds and was consistent.

On arrival to the RR all patients were given O_2 and the study was terminated. Patients who were coughing or remained intubated or on whom the sensor came apart during transport were excluded from the study. Data obtained were first analyzed using one factor analysis of variance. Then Tukey's Studentized Range test was used to determine which group was significantly different.

Results. Results are shown in Table I and II. SaO_2 was 100% in all patients before moving from the OR. MEAN SaO_2 during transport for all patient groups was 93.5 ± 0.55% with a range of 82-100%. MEAN saturation ranged 88.12-1.2% in Group I; 91.8 ± 1.0% in Group II and 95.39 ± 0.47% in Group III. The analysis of variance revealed significant differences among the three group means. Group comparison is shown in Table II for differences in means and all the values are significant at the 0.05 level.

Conclusions In spite of three minutes postanesthetic oxygenation young infants desaturate rapidly during transfer to the RR. This is most notable in the 0-6 month age group followed by the 7 month - 12 month age group and least in the 13 month - 14 year age group. The infants pulmonary physiology is different in many respects from older children and these differences make him more prone to hypoxia. Instability of the small airways with closure withing the tidal volume due to lesser elastic recoil and diminished distensibility of the lungs occur in infancy even without the effect of general anesthesia.[3] In addition during and after halothane anesthesia chest wall expansion is altered through intercostal muscle inhibition, ribcage retraction, and the unopposed action of the diaphragm. The combination of these factors distorts the chest wall and contributes to lower lung volumes.[4,5] All these changes are most marked in the youngest patients. Pulse oximetry is a simple method to quantitate the resulting desaturation. Rapid transport to the RR on supplemental oxygen is recommended to avoid potential hypoxia in the very young.

References.

1. Motoyama EK, Glazener CH; Hypoxemia after general anesthesia in children. Anesth Analg 1986;65;267-72.
2. Marshall BE, Wyche MQ; Hypoxemia during and after anesthesia. Anesthesiology 37:178-209, 1972.
3. Mansell A, Bryan C, Levison H; Airway closure in children. Journal of Applied Physiology 1972:-Vol.33, No. 6;711-714.
4. Tusiewicz K, Bryan A. Charles, Froese AB; Contributions of changing rib cage-diaphragm interactions to the ventiltory depression of halothane anesthesia. Anesthesiology 47:327-337, 1977.
5. Muller NL, Bryan A. Charles, Chest wall mechanics and respiratory muscles in infants, Pediatric Clinics of North America:Vol.26,No.3, Aug.1979;503-516.

Table I
SaO_2 During Transport from OR to RR

	Minimum Value	Maximum Value	MEAN	SEM
Group I 0-6M n=10	82.0	93.0	88.1*	1.20
Group II 7M-12M n=10	85.0	97.0	91.8*	1.0
Group III 13M-14Yr. n=40	89.0	100.0	95.3*	0.47

*P<0.0001

Table II
Tukey's Studentized Range Test for Saturation

Group Comparison	Difference Between MEAN
III-II	3.59*
III-I	7.29*
II-I	3.70*

*Significant @ 0.05 Level.

Title: DISTRIBUTION OF ARTERIAL AIR EMBOLI: EFFECT OF THE TRENDELENBERG POSITION IN DOGS

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Introduction. Arterial air embolism is a potentially lethal complication following cardiopulmonary bypass (CPB), decompression sickness and pulmonary barotrauma. Morbidity and mortality are related to the degree and location of occlusive air bubbles within the systemic circulation. Treatment modalities include 100% oxygen ventilation, steroids, barbiturates, the Trendelenberg position with or without retrograde perfusion, and hyperbaric compression if available (1). The rationale for use of the Trendelenberg position is based on the premise that the buoyant properties of air bubbles will prevent their distribution to the brain. In this study we examined the distribution of bubbles in the arterial circulation following left ventricular and ascending aortic air injection in dogs.

Methods. Sixteen dogs (14-31 kg) were divided into two groups of 8. The first received air injections into the left ventricle and the second into the ascending aorta. The dogs were anesthetized with thiopental (25 mg/kg) and maintained with halothane or isoflurane (0.8 or 1.5%) in oxygen (30%) and nitrogen (balance). Pressure monitoring catheters were placed in the abdominal aorta (BP) via the right femoral artery, pulmonary artery (PAP) via the right jugular vein and left ventricle (LVEDP) via the right carotid artery.

The left common carotid artery was exposed 4 cm below the level of the thyroid for placement of an ultrasonic Doppler probe (100 mHz, Parks) for detection of carotid artery bubbles passing into the cerebral circulation. A second Doppler probe was placed directly over the suprarenal aorta via an abdominal midline incision to detect arterial bubble distribution away from the head. Ultrasonic signals were filtered and amplified for chart recording and audio detection.

The animals in group 1 received 0.5 or 1.0 ml air injections into the left ventricle at rates of 1 ml/sec. The injections were conducted twice at 0°, 10°, and 15° Trendelenberg position. The animals were placed in a supine position on the surgical table and the table was adjusted according to the angle desired. The Doppler recorded the presence of carotid artery and aortic bubbles. In the second group a left thoracotomy was performed between the 5th and 6th ribs to gain access to the ascending aorta. The pericardial sac was resected and the ascending aorta located for manual verification of the catheter tip. The left ventricular catheter was then withdrawn to a location approximately 3 cm above the aortic valve. In this series of experiments the left ventricular catheter was a multi-lumen catheter with a side port, used for injection of the air emboli located 1 cm below the tip. The air injections were identical to those described in group I. A control injection of saline preceded the air injections in 10 animals.

Results. The air bubbles were detected by the Doppler probes at both sites in every case. (Table 1). On the Doppler, audible signals were less at 15° Trendelenberg than at 0° or 10°. However, bubbles were detected in all dogs at 15°. Rate, site and size of the arterial air injections did not affect the results.

Discussion. The rationale for use of the (steep) Trendelenberg position in arterial air embolism is based on early work from Van Allen (1929) (2) and misinterpretation of the case report by Atkinson (1983) (3) about a diving casualty. For this procedure to be effective, the force of buoyancy manifested by the bubbles would have to be sufficient to overcome the force of flowing arterial blood. This was not found to occur in any of the embolizations from this study. From this we suggest that the Trendelenberg position is ineffective in preventing air emboli from reaching the cerebral circulation.

References.

1. Brenner WI. A battle plan in the event of massive air embolism during open heart surgery. The Journal of Extra-Corporeal Technology 1985; 17:133.
2. Van Allen M., Hardina L and Clark J; Air embolism from the pulmonary vein. Archives of Surgery 1929; 19 (4): 567.
3. Atkinson JR. Experimental air embolism. Northwest Medicine 1963; 62:699.

% WITH CAROTID BUBBLES

INJECTION SITE: TRENDELENBERG	LEFT VENTRICLE	ASCENDING AORTA
0°	100	100
10°	100	100
15°	100	100

Title: Neuroendocrine Response to Prolonged Isoflurane Anesthesia for Reconstructive Surgery

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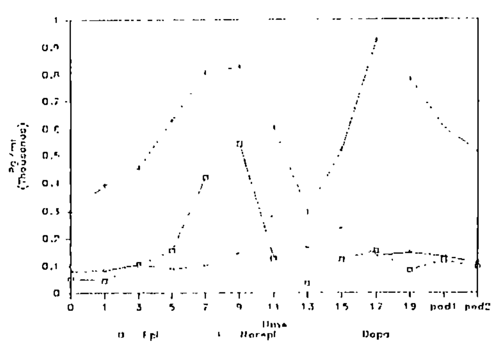
Introduction. The need for anesthetics longer than seven hours has increased with the advent of microvascular reconstructive surgery. Isoflurane in 50% N20/02 is frequently used as the maintenance anesthetic during such prolonged anesthetics. This study was designed to evaluate the effects of prolonged isoflurane anesthesia on the neuroendocrine system.

Methods. Fifteen patients (13 males and 2 females) having elective reconstructive surgery consented to the study, which was approved by the Institutional Research Review Committee. Age range was from 18-74 years and weight ranged from 47-87 kg. All were in general good health and were on no preoperative medications. The day prior to surgery blood was drawn for baseline antidiuretic hormone (ADH), epinephrine (Epi), and norepinephrine (NE), and dopamine (Dopa) levels. All patients received similar preoperative sedation with morphine sulfate and diazepam one hour prior to induction. Induction was accomplished with sodium pentothal (3-5 mg/kg) and intubation was facilitated with vecuronium (0.1 mg/kg). Isoflurane (0.5-1.1 MAC in 50% N20/02) was used for maintenance. Intraoperative fluid and blood replacement was titrated to ongoing losses, hematocrit (hct $<$ 28), mean arterial pressure (MAP $<$ 80), and urine outout (UOP $<$ 0.5 ml/kg/hr). After induction, plasma NE, Epi, Dopa, and ADH concentrations were measured every two hours intraoperatively, at the end of surgery, and at 24 and 48 hours postoperatively. Student-Newman-Keuls method was used for stastical analysis of individual variables and Pearson correlation coefficient for correlations between variables. Blood pressure, heart rate, and central venous pressure were measured every 30 minutes in all patients and eight patients had pulmonary artery catheters enabling us to measure cardiac output and wedge pressure at the same intervals.

Results. Average surgical time was 11.1 hours. Estimated blood loss was 26.30 ml±1696 (SD). Total intraoperative fluid administration (isotonic crystalloid, 5% albumin, packed red blood cells) averaged 1000 ml/hr. Average UOP ranged from 0.5-2.5 ml/kg/hr. Intraoperative MAP was 82±1 mmHg (Range: 76-88). Intraoperative cardiac output was 5±.8 L/min and wedge was 6.6±2 mmHg. Intraoperative elevations occurred in NE, Epi, Dopa and ADH that were equal or greater than those reported with major abdominal surgery with isoflurane, N20/02[1] (See Table 1 and Fig 1&2). A correlation was found between the elevated serum levels of ADH and the serum concentrations of both NE and E at the 5th, 7th, 9th hours and at the end of surgery ($p < .01$).

Fig 1



Discussion. A previous study has demonstrated that isoflurane in N20/02 alone was unable to suppress the neuroendocrine responses to surgical stress.[1] Our study shows that although heart rate and blood pressure did not reflect a stressed patient, sufficient stimulation occurred during microvascular surgery to cause catecholamine elevations as high or higher than with intra-abdominal surgery. Furthermore, the greatest stress occurs after the sixth hour when hemodynamics tend to be very stable. The influence of these increased levels of catecholamiens and ADH for a prolonged period of time may have adverse effects.

References.

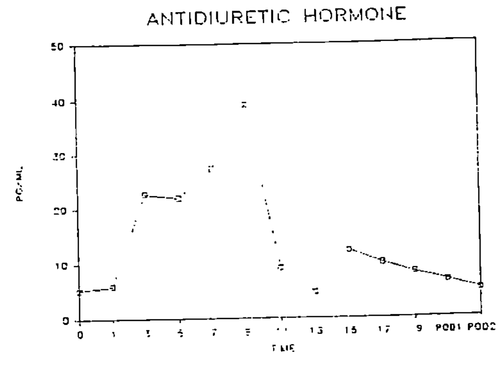
1. Gelman S, Rivas JE, Erdemir H, et al: Hormonal and haemodynamic responses to upper abdominal surgery during isoflurane and balanced anesthesia. Can Anaesth Soc J 1984; 31:509-16.

Table 1.

	MEAN	SEM	RANGE
ADH (2-5 pg/ml)	15.53	± 3.32	4.77- 37.00
EPI ($<$45 pg/ml)	178.60	± 50.79	35.75- 543.50
NOREPI ($<$ 296 pg/ml)	592.10	± 72.86	295.00-1032.00
Dopamine ($<$100 pg/ml)	140.6	± 16.69	88.53-280.5

For all values, $p > 0.05$.

Fig 2



Title: SUBDURAL BLOCK FOLLOWING EPIDURAL INJECTION OF LOW-DOSE BUPIVACAINE

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Introduction. The extra-arachnoid subdural space is a potential space between dura and the arachnoid membranes. It contains a small amount of serous fluid which moisten the surface of the opposed membranes. Accidental injections of local anesthetics into the subdural space when performing an epidural block is an unusual complication with an estimated incidence of 0.1%.

The features of a subdural block are: 1) unexpected wide-spread segmental block following attempted epidural injection, 2) slow onset of symptoms similar to a spinal block such as motor blockade with low concentration of bupivacaine (eg .125% - .025%), 3) extensive sympatholysis out of proportion to the administered doses of local anesthetic, and 4) delayed recovery.

By comparison, accidental total subarachnoid injection may have a variable onset, but characteristically involves sudden cardiovascular collapse and severe respiratory depression and pupillary dilatation.

At our institution, approximately 800 epidural injections of combination of local anesthetics and steroids are given each year at the Pain Center for various forms of lower back problems. We report 18 cases of suspected subdural injection over the past 2 years out of our sample population of 1600.

Methods. The patient population consisted of approximately 1,600 outpatients, over a two-year period, who were referred to the Pain Center for lumbar epidural steroid injections secondary to various forms of lower back pathology. All patients received single injections into a lumbar interspace of bupivacaine (5-10cc of 0.125% - 0.25%), in combination with Depo-Medrol^R 80-120 mg. Blocks were performed by an attending anesthesiologist or a supervised resident. Epidural spaces were identified by the loss of resistance technique with either a 17 or 18 gauge Touhy needle positioned from the interspaces of L2-L5, with negative aspiration.

After the injection, the patients were observed for approximately 1 hour prior to release.

Results. Criteria used for classification of a subdural injection included delayed onset (longer than 15 mins) of an extensive sensory and some degree of motor block, negative CSF aspiration, and one or more of the following: presence of moderate hypotension defined as 20-30% drop from baseline, slow progressive respiratory embarrassment and incoordination, and/or delayed recovery. Eighteen of the 1600 patients, an incidence of 1.125%, met our criteria, and therefore, a subdural injection was assumed to have been responsible for their clinical course.

Discussion. Epidural blocks occasionally exhibit atypical patterns of spread which can be explained by relative overdose, too rapid of an injection or an injection into the subarachnoid or subdural spaces. Several investigators have demonstrated radiological confirmation of catheters present in the subdural space in cases of apparent "massive epidurals". There are subtle differences that distinguish subdural blocks from other causes of atypical spread. For example, in several series of radiologically confirmed epidural catheter placement where "massive epidural" resulted, the clinical course was generally milder than subdural blocks. Apnea, unconsciousness, or severe hypotension did not occur, although sensory loss to C6 has been noted. The characteristic features of a subdural block have been described and contrasted to high subarachnoid blockade.

The extra-arachnoid subdural space is a potential space between the dura mater and arachnoid mater just as the epidural space is a potential space between the dura mater and the ligamentum flavum. It does not communicate with the subarachnoid space, but is continued for a short distance on the cranial and spinal nerves. It is larger in the cervical than lumbar area. It is in free communication with the lymphatic spaces of the nerves. The extra-arachnoid subdural space can be demonstrated by radiologists during the performance of a myelogram. They are careful not to inject into this area as contrast medium deposited in the subdural space can obscure the diagnostic field.

We believe from our experience that the incidence of subdural block is higher than previously reported. This may be especially true in patient populations where there is a high incidence of previous back surgery.

Conclusion. Following a subdural injection of local anesthetic, onset of development of an extensive sensory and motor block with possible hypotension and respiratory embarrassment may occur more than 30 minutes after the injection. There is anatomic evidence that the subdural space exists and should be considered when there has been extensive spread of an epidural block with small volume and dilute concentrations of local anesthetic. We also recommend that outpatients receiving epidural injections with even low doses of local anesthetics be observed for at least 1 hour before discharge.

References

1. Manchanda, et al: Unusual clinical course of accidental subdural local anesthetic injection. Anesth Analg 1983;62:1124-6.
2. Melt M, Maher N: Injection into the extra-arachnoid subdural space. Anaesthesia 197732:7[illegible]-766.
3. Boys TE, Norman PK: Accidental subdural analgesia. Br J Anaesth 1974;47:1111-1113.
4. Soni [illegible], Holland R: An extensive lumbar epidural block. Anaesth Inten Care 1981;9:150-152. 5. Williams & Warwick. Gray's Anatomy. 36th Edition. 1049-1051.

Title: CHANGES IN PvO_2 OF CUTANEOUS VEIN DURING SPINAL ANESTHESIA

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Introduction. In a previous study[1] increased cutaneous blood flow to an affected digit following sympathetic denervation increased pulse volume amplitude (PVA) of a photoelectric plethysmograph (PEPG). Increased PVA of the toe following spinal anesthesia began to decrease when the sensory level receded below T-10.[2] In a further study on the circulatory kinetics of PVA of the PEPG, the PVA results from the pulsating venous flow generated by shunting of the arterial pulse via open arteriovenous (AV) anastomoses.[3] Since AV shunting is controlled by sympathetic tone, sympathetic denervation and recovery during the course of spinal anesthesia should accordingly change the PvO_2 of the superficial vein of the foot.

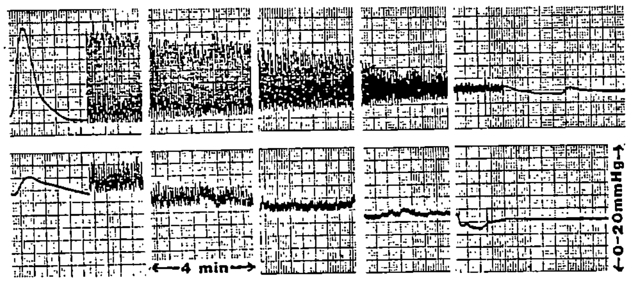
Methods. The study was approved by the institutional review board for human studies. Twenty six consenting patients who underwent transurethral resection of the prostate under spinal anesthesia were divided into two groups according to sensory levels measured in the recovery room. The sensory levels of Group A (20 patients) and Group B (6 patients) were T-10 or above and T-11 or 12, respectively. Their mean age was 72.4. A superficial vein of the foot or the saphenous vein at the ankle was retrogradely cannulated with a 22 gauge catheter. The catheter was kept open with a heparin lock. Spinal anesthesia was achieved in the sitting position with tetracaine, 10-12 mg. All patients breathed room air throughout the study period. The bladder was continuously irrigated postoperatively with normal saline. Through the catheter, blood samples were drawn to measure PvO_2 at the following times: before spinal anesthesia was administered, after sensory level was determined with the pin-prick method, when sensory level receded to T-11 or 12, and when the patient was able to lift his hip (motor recovery). In one additional patient, a superficial vein on the great toe was retrogradely cannulated after spinal anesthesia. In addition to the measurements of PvO_2, venous pressure was measured via the catheter with a pressure transducer placed on the toe in a supine patient. Also, PVA of the adjacent toe was monitored using a PEPG. Both tracings of venous pressure and PVA were simultaneously recorded.

Results. These are summarized in the Table and Figure below.

Table. PvO_2 Values (mmHg) During Spinal Anesthesia

	Group A (N = 20)	Group B (N = 6)
Prespinal Control	38 ± 11.6	34.5 ± 5.5
T-10 or Above	67 ± 8.8	-----
T-11 or 12	42 ± 9.6	34.8 ± 9.5
Motor Recovery	36 ± 7.0	29.0 ± 8.0

Values are Mean ± SD. Changes in PvO_2 in Group A are significant (One-way analyses variance). The figure shows simultaneous recordings of PVA (upper tracing) and pulsatile venous pressure (lower tracing) of the toe. The pulsatile venous pressure shows a mean pressure, 15 mmHg, and a pulse pressure, 3 mmHg, at sensory level T-9. As the sensory level recedes below T-10, the venous pulse pressure gradually narrows until it becomes a flat line with a mean pressure of 8 mmHg. The narrowing pulse pressure matches with decreasing mean pressure and PVA. The values of PvO_2 decreased from 73 to 49 mmHg during the period.



Discussion. Cutaneous blood flow subserves tissue nutrition and thermoregulation. The blood flow for nutrition is an insignificant fraction of the skin flow. However, cutaneous flow can vary from 1 to as much as 150 ml/100 g/min in response to thermoregulatory stimuli. These variations are possible because blood can be shunted through AV anastomoses into subdermal venous plexuses. The AV anastomoses are innervated by sympathetic vasoconstrictor fibers; therefore, PvO_2 will be changed depending upon the sympathetic tone. Also, clinical signs of sympathetic denervation such as increased skin temperature, hyperemia, and venodilation can be readily explained by the AV shunting. Increased flow via subdermal venous plexuses with shunted arterial blood should cause a rise in skin temperature, hyperemic skin, and venodilation. Evidence presented in the study confirms that sympathetic recovery initiates when sensory level recedes below T-10. According to known anatomy, complete sympathetic denervation of the lower limb requires blockade of entire preganglionic fibers, T-11 through L-2. If some preganglionic fibers recover from spinal anesthesia, recovery of postganglionic fibers should be more diffuse because of extensive overlapping in postganglionic innervation. Bladder filling and/or spasm caused by continuous irrigation could enhance sympathetic responses in the partially recovered sympathetic system at sensory level T-11 or 12. In summary, PvO_2 in the superficial vein of the foot significantly increased following spinal anesthesia if the sensory level attained T-10 or above. However, values of PvO_2 at the sensory level of T-11 or 12 were not significantly different from prespinal control values. It is postulated that enhanced AV shunting by sympathetic denervation increases PvO_2 and sympathetic recovery begins when sensory level recedes below T-10.

References.

1. Kim J-M, Arakawa K, VonLintel T. Use of the pulse-wave monitor as a measurement of diagnostic sympathetic block and of surgical sympathectomy. Anesth Analg 1975; 54:289-96.
2. Kim J-M, LaSalle AD, Parmley RT. Sympathetic recovery following lumbar epidural and spinal analgesia. Anesth Analg 1977; 56:352-5.
3. Kim J-M, Arakawa K, Benson KT, Fox DK. Pulse oximetry and circulatory kinetics associated with pulse volume amplitude measured by photoelectric plethysmography. Anesth Analg; in press.

Title: INPATIENT VS. DAY SURGERY: DIFFERENCES IN RESOURCE USE, PATIENT VOLUME AND ANESTHESIA REIMBURSEMENT

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Introduction. Fixed-price payment methods (including DRGs) encourage hospitals and physicians to identify the most efficient modes of delivering patient care and to maximize patient volume. For surgical patients, ambulatory care is believed to be more efficient than inpatient care, though little data are available to support this belief. This study examined resource use and the patient volume implications among comparable patients who received inpatient (INPT) or Day Surgery Unit (DSU) care in our institution.

Methods. We reviewed the charts of all INPTs and DSU patients who underwent surgical arthroscopy of the knee or diagnostic laparoscopy in the period January-June 1984. During this period, insurers did not require that these procedures be performed on an ambulatory basis. In addition, because of DSU scheduling delays, surgeons frequently scheduled DSU candidates for INPT care. Information on patient age, ASA physical status, surgical procedure and attending surgeon was collected from patient charts to assess the comparability of the INPT and DSU patient groups. Diagnostic laparoscopies were classified in two groups: level I included examination only of the pelvic viscera, level II also included fallopian tube lavage. Data on four hospital resources (preoperative tests, time in the operating and recovery rooms, and analgesic medications administered in the recovery room) were also collected from patient charts. Chi-square tests and Z-tests were used to determine the significance of differences between groups.

Results. Two hundred eighty-four patients were included in the study. There were no significant differences in mean patient age, physical status, surgeon or anesthesia team between INPTs and DSU patients undergoing each surgical procedure. All patients had preoperative CBCs and urinalyses. However, a significantly higher percentage of INPTs had preoperative chest x-rays, ECGs, Panel 6 tests and PT/PTT determinations than did DSU patients (Table 1). This lower preoperative testing rate for DSU patients may be attributed to a preoperative testing algorithm specified by DSU anesthesiologists but not used in the INPT ORs. Mean total operating room time was significantly longer for INPTs than for DSU patients (p<.002). Mean recovery room time was longer for DSU patients than for INPTs (p<.002). A significantly higher percentage of INPTs received analgesic medication in the recovery room than did DSU patients (p<.02). Notably, all INPT recovery room analgesics were IV narcotics while only 12% of the DSU analgesics were parenteral narcotics. For surgical arthroscopies, the difference in operating room time translated to a lost opportunity of 1.8 INPTs and $248-$466 in anesthesia payments per operating room per day, depending on the reimbursement scheme (Table 2).

Discussion. This study compared intrainstitutional differences in the use of four hospital resources. For comparable groups of patients, far fewer preoperative tests and recovery room analgesics were used in the DSU. Nurse and aide labor costs (calculated from OR and RR times) were also lower in the DSU ($8 to $24 per case). These analyses support the premise that day surgery may be more resource-efficient than inpatient care and also provide information with which anesthesia and surgery departments and institutions can reasses their inpatient practices.

Table 1.
Percent of INPTs and DSU patients with each preoperative test per surgical procedure.

Preop Test	Surgical Arthroscopy		Level 1 Laparoscopy		Level 2 Laparoscopy	
	INPT	DSU	INPT	DSU	INPT	DSU
N =	61	62	24	49	42	46
Chest X-ray	39% *	12%	58% *	24%	79% *	0%
ECG	30% **	11%	50% *	12%	83% *	2%
Panel 6	92% *	3%	75% *	0%	86% *	2%
PT/PTT	41% *	2%	25% *	2%	2%	0%

*p .01
**p .05

Table 2.
Estimated number of surgical arthroscopy patients and anesthesia reimbursement per seven-hour operating room shift (based on statewide Blue Shield rate).

	INPT	DSU
Mean OR time	128 min	83 min
Turnaround time	30 min	10 min
Number of patients	2.8 patients	4.6 patients
Time-based payment	$943	$1,191
Fixed-price payment	$725	$1,191

Title: OMISSION OF NITROUS OXIDE DOES NOT DECREASE THE INCIDENCE OR SEVERITY OF EMETIC SYMPTOMS AFTER ISOFLURANE ANESTHESIA

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Introduction. It has been postulated that administration of nitrous oxide is associated with high incidence of postoperative nausea and vomiting but no well controlled studies have been carried out to demonstrate this (1). The aim of this study was to find out whether and to what extent nitrous oxide contributes to the occurrence of emetic symptoms after isoflurane anesthesia. The incidence of nausea and vomiting was compared after general anesthesia with isoflurane-air-oxygen to those after isoflurane-nitrous oxide-oxygen anesthesia.

Methods. One hundred and ten patients scheduled for abdominal hysterectomy were entered. The study protocol was approved by institutional ethical committee and informed consent was obtained from each patient for the study. Only patients in ASA I or II groups and between ages 35 to 55 years were studied. Patients were randomized according to their date of birth to receive either nitrous oxide or air. The person evaluating the emetic symptoms was not aware of the method of anesthesia used. Patients were premedicated with meperidine 1 mg/kg 40 to 60 min before anesthesia. After insertion of i.v. cannula and start of i.v. infusion (Ringers solution) 1.5 mg of alcuronium chloride, 0.2 mg of glycopyrrolate and 0.1 mg of fentanyl was administered into the stream of the i.v. solution. Two minutes later anesthesia was induced with 4 mg/kg of thiopental. Oral endotracheal intubation was facilitated with 1.5 mg/kg of succinylcholine and anesthesia was maintained in random order either with isoflurane in nitrous oxide and oxygen (30%) or with isoflurane in air and oxygen (30%). Starting inspired concentration of isoflurane was 1% for those receiving nitrous oxide and 1.5% for those not receiving nitrous oxide. Thereafter isoflurane was administered according to clinical needs its concentration being changed if systolic blood pressure or heart rate changed more than 25% from baseline. Average inspired isoflurane concentration was estimated from the anesthesia chart for both groups. Fentanyl was used as an adjunct to isoflurane anesthesia and was given in a standardised way 0.05 mg every 45 minutes. Alcuronium was used to maintain neuromuscular blockade; 20 to 25% of the patients´ muscle power was maintained as assessed with neurostimulator. End-tidal CO_2 was continuously measured with a capnometer to ascertain normoventilation in both groups. At the end of anesthesia glycopyrrolate 0.4 mg and neostigmine 2.0 mg were given i.v.. Oxycodone chloride was used for postoperative pain and droperidol for emetic symptoms when needed in both groups. The incidence of emetic sequelae was determined for the first 24 hours after operation at different intervals: 0 to 2, 2 to 6, 6 to 12, 12 to 18 and 18 to 24 hours as in our previous studies (2,3). At the end of each interval a trained nurse registered whether retching or vomiting had occurred and asked the patient whether she felt nauseated. Student´s t-test and chi-square test were used for statistics.

Table 1. Summary of findings (mean±SD) in patients undergoing abdominal hysterectomy under isoflurane-air-oxygen (Air-O_2) or isoflurane-nitrous oxide-oxygen (N_2O-O_2) anesthesia.

	Air - O_2	N_2O - O_2
Patients		
n	55	55
Age (yr)	42±4	43±5
Weight (kg)	66±10	66±12
Height (cm)	165±5	163±6
Duration of anesth. (min)	103±36	102±31
Average inspired isoflurane conc. (%)	1.4±0.2	1.1±0.2
Oxycodone for postoperative pain (mg)	59±12	57±17
Emetic symptoms during 24 h (%)		
none	38	33
nausea	33	33
retching	16	18
vomiting	13	16
Patients given droperidol (%)	44	55

Results. Characteristics of patients and summary of findings are presented in Table 1. The groups are constituted similarly. No difference was found during any time interval studied in the incidence or severity of emetic symptoms between the two anesthetic techniques used. The percentage of patients given droperidol for emetic symptoms was similar in the two groups, as well.

Discussion. The method used to assess postoperative emetic symptoms has previously proved sensitive in evaluating of the effects of antiemetic drugs on the incidence and severity of postoperative nausea and vomiting (2). In this study omission of nitrous oxide from routine anesthetic technique did not decrease the incidence or severity of postoperative emetic symptoms. It is concluded that nitrous oxide does not contribute to the occurrence of emetic symptoms after isoflurane anesthesia.

References.

1. Eger EI II. Should we not use nitrous oxide? In Nitrous oxide, ed Eger EI II. New York: Elsevier Publishing Company Inc, 1985; 339.
2. Korttila K, Kauste A, Auvinen J. Comparison of domperidone, droperidol, and metoclopramide in the prevention and treatment of nausea and vomiting after balanced general anesthesia. Anesth Analg 1979; 58:396.
3. Korttila K, Kauste A, Tuominen M, Salo H. Droperidol prevents and treats nausea and vomiting after enflurane anaesthesia. Eur J Anaesthesiol 1985; 2:379.

Title: SUFENTANIL VERSUS FENTANYL: HEMODYNAMIC EFFECTS IN VALVULAR HEART DISEASE

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Introduction. Sufentanil (S) has been reported to provide complete anesthesia with minimal effects on cardiovascular variables.[1] Previous reports using doses of 15 µg/kg in patients with coronary disease significantly decreased systolic pressure and peripheral resistance prior to surgical incision,[1] although doses of 8-30 µg/kg anesthesia have been recommended. In an attempt to avoid hypotension, we randomly compared the cardiovascular and endocrine effects of S, 5 µg/kg, and, as S is 4-5 times more potent than fentanyl (F), an F dose of 25 µg/kg in 17 consenting patients with valvular heart disease.

Methods. Premedication was morphine 0.1 mg/kg and scopolamine .005 mg/kg IM 1 hour prior to study. Peripheral intravenous infusions of 5% dextrose were placed to ensure venous patency. Radial and pulmonary artery catheters were inserted using local anesthesia. Control measurements of systolic (SAP), diastolic (DAP), mean arterial pressure, heart rate and rhythm, pulmonary artery systolic, diastolic, mean and wedge pressure, central venous pressure, arterial blood gases, and plasma catecholamines were made with the patient spontaneously breathing 100% oxygen. Thermodilution cardiac outputs were performed in triplicate. Systemic (SVR) and pulmonary vascular resistance (PVR) and left ventricular stroke work index (LVSWI) were calculated with standard formulas. Plasma norepinephrine and epinephrine were determined by high performance liquid chromatography.

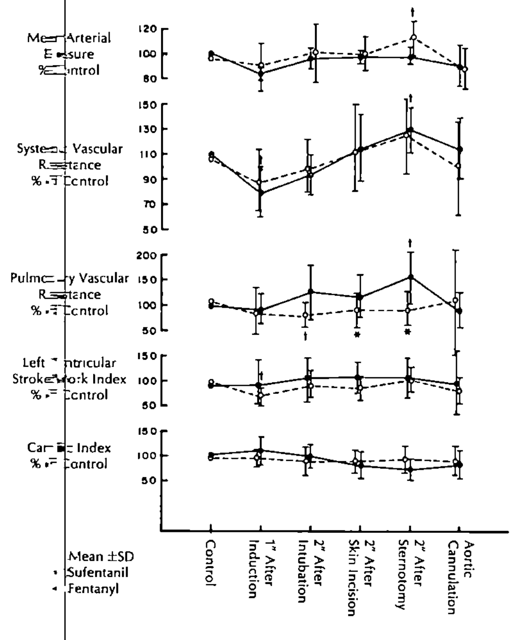
After control measurements, metocurine, 6 mg, was given IV to prevent chest wall rigidity during subsequent narcotic administration. S, 5 µg/kg, or F, 25 µg/kg, were then given IV over 2-3 min and all variables repeated 1 min after induction. Ventilation was controlled to maintain pCO_2 at or near 40 mmHg. After these measurements, metocurine, 0.22 mg/kg, was given. Additional measurements were made at 2 min after incision, 2 min after sternotomy and aortic cannulation. Additional doses of S, 50-150 µg, or F, 250-300 µg, were given for hemodynamic changes of 15% over control or signs of light anesthesia. Statistical analysis of variance was performed on the data as directly measured and as % of control.

Results. There were 5 patients with aortic and 4 with mitral valve disease in F group. There were 3 patients with aortic and 5 with mitral valve disease in the S group. When compared to control, MAP decreased significantly on induction and at aortic cannulation in the F group. Cardiovascular variables were unchanged by induction or maintenance of anesthesia with S except for an increase in PVR and SVR and a decrease in CI at sternotomy.

When the two groups were compared to each other as % of control, PVR increased in S patients at skin incision (124% vs 88% in F patients, $p<.05$) and sternotomy (157% vs 92% in F, $p<.05$). While LVSWI decreased on induction with F, SVR and PVR in the S group and MAP in the F group increased significantly at sternotomy (Figure). There were no differences between groups in catecholamines, but considerable variability was present.

All S patients achieved complete anesthesia with the 5 µg/kg induction dose. In contrast, three F patients were responsive to command after fentanyl induction and required lorazepam (2) or thiopental (1) to prevent apparent awareness after the 25 µg/kg F dose. Isoflurane was required to control sternotomy hypertension in 2 other patients in the F group, one of whom required lorazepam during sternotomy to prevent awareness.

Discussion. This study indicates that induction of anesthesia with either S (5 µg/kg) or F (25 µg/kg) produces minimal hemodynamic changes, but anesthesia was not consistently complete with F. Incomplete anesthesia with responsiveness to command occurred in 33% of F patients. Similar results were noted by Bailey in that 26% of patients were not unconscious with a 30 µg/kg dose.[2] Unlike fentanyl, reliable, more complete anesthesia without undesirable hypotension can be achieved with induction doses of sufentanil, 5 µg/kg. PVR increased on incision and sternotomy in patients receiving sufentanil. Additional S doses might attenuate this increase in PVR with surgical stimulation. However, because MAP and CI were unchanged, the increased PVR appears to have minimal clinical significance.



* p<.05 Compared to Fentanyl
† p<.05 Compared to Control

Reference.
1. Bovill JG, et al. Comparison of fentanyl, sufentanil, and alfentanil anesthesia in patients undergoing valvular heart surgery. Anesth Analg 1984; [illegible]:1081-6.
2. Bailey PL, et al. Anesthetic induction with fentanyl. Anesth Analg 1985; 64:48-53.

TITLE: MONITORING OF SOMATOSENSORY EVOKED POTENTIALS DURING CAROTID ENDARTERECTOMY

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Intraoperative monitoring of somatosensory evoked potentials (SSEP)[1] may be useful during carotid endarterectomy. However, no critical comparison with EEG monitoring has been made and no criteria for interpretation of SSEP changes have been defined. We report here our experience with simultaneous monitoring of SSEP and conventional EEG in a series of patients undergoing carotid endarterectomy.

Materials and Method. The study was approved by institutional Ethics Committee. Thirty-four consecutive patients undergoing carotid endarterectomy were studied. All patients were induced with thiopental, fentanyl and succinylcholine and maintained on 50% nitrous oxide and isoflurane (32) or halothane (2) and pancuronium. Monitoring included end-tidal CO_2 and nasopharyngeal temperature. Sixteen channel EEG was recorded in the conventional manner using standard montage. SSEP was recorded from the somatosensory cortex (C3' or C4') ipsilateral to the surgical site as well as over C_7 spine. Both EEG and SSEP were recorded prior to cross-clamping of the carotid artery, continuously during cross-clamping, and again following release of the clamp. Recognizing the influences of inhaled anesthetics on SSEP, the inspired concentration was limited to 1% and was less than 0.5% in most instances. As well, attempts were made to ensure that anesthetic depth was constant during the recording periods. Whenever feasible stump pressure was also recorded. Postoperatively, the patient was examined for development of new neurological deficits. SSEP recordings were analyzed using both the amplitude of the cortical peak (N20) and central conduction time (CCT). Changes observed during cross-clamping were correlated with EEG changes and postoperative neurological deficits.

Results. Satisfactory SSEP and EEG recordings were obtained in 31 patients, and stump pressure was measured in 29. Mean age of the patient was 64±8 (SD), the occlusion time was 36±11 mins and the $PaCO_2$ was 40±3 mmHg. The mean stump pressure was 48±14 mmHg. The mean isoflurane concentration used during cross-clamping was 0.4±0.2%. The significant findings are summarized in Table 1. Twenty-one patients had stable SSEP throughout the procedure and none had EEG or developed new neurological deficits. To facilitate interpretation of SSEP, criteria were established for categorization depending on whether the major change was in amplitude, central conduction time or both. Three patients had significant reduction of amplitude with cross-clamping and in two of these patients simultaneous EEG changes were observed. Two patients in this group also developed transient new neurological deficits in the recovery room, but only one of these two had EEG changes. Four patients had increase of CCT > 1 msec, but in two patients this was of a transient nature lasting less that 5 minutes despite continued cross-clamping. In one patient this reversed with the release of the cross-clamp while the remaining patient demonstrated only partial recovery and this correlated with persistent changes in EEG. No patient in this group developed any new neurological deficits. In the remaining three patients who demonstrated a major SSEP change, this was of a transient nature in two, and reversible in one. None developed EEG changes and only one patient developed a transient neurological deficit.

Discussion. Our study demonstrated that (1) the incidence of stroke following carotid endarterectomy in this series was extremely low; only 3 patients developed neurological deficits in the recovery room and all were of a transient nature. This was in spite of the fact that no action was taken based on either SSEP or EEG changes. (2) Comparing SSEP changes and EEG changes, and correlating these with new neurological deficits, no clear cut advantages of SSEP monitoring could be demonstrated. In patients who had unchanged SSEP during cross-clamping, there was perfect correlation with EEG monitoring and absence of postoperative neurological deficits. In patients who developed SSEP findings, it was evident that transient changes were not important, and that reduction in amplitude > 50% was a better criterion to use than changes in CCT. Perhaps one can argue that SSEP monitoring is marginally better than EEG monitoring since all patients who develped new transient neurological deficits had developed reversible SSEP changes but not all had EEG changes. We conclude that if SSEP monitoring is to be used for intraoperative monitoring of cerebral function during carotid endarterectomy, the criterion of 50% reduction in amplitude should be used and that transient changes are of no consequence.

Reference

1. Markand ON, Dilley RS, Moorthy SS, Warren C. Monitoring of somatosensory evoked resonses during carotid endarterectomy. Arch Neurol 1984;41:375-378

SSEP CHANGES			EEG CHANGES	NEW NEUROLOGICAL DEFICITS	STUMP PRESSURE (mmHg)
I Unchanged	21		0	0	50±13
II ↓ amp > 50%	3	(R)	2(R)	2(T)	15,19,38
III ↓ CCT > 1 msec	4	(2T)	1(T)	0	42,55
		(1R)	0		77
		(1P)	1(P)		37
IV ↓ amp > 50% and ↓ CCT > 1 msec	3	(2T)	0	0	36,50
		(1R)	0	1(T)	54

T = transient changes that resolved spontaneously without release of clamp
R = changes that reversed with release of clamp
P = persistent changes

Title: CATARACT OPERATION - INPATIENT OR OUTPATIENT?

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Introduction. An increasing geriatric population has made the operation for senile cataract more common. Perioperative psychological problems, consisting mainly of preoperative fear, postoperative confusion, poor memory, and inability to concentrate, often occur. An increasing bed shortage has made it popular to do cataract operations on a day bed basis. There is concern that delayed mental recovery of these patients, makes it unsafe to discharge them the same day as their operation. This study was done to assess the mental recovery of elderly patients post cataract operation under local anaesthesia and sedation.

Method. This study was approved by the Human Experiments Committee of University of Toronto. Ninety alert and oriented patients, over 60 years of age (mean age 73.15 years), scheduled to undergo cataract operation under local anaesthesia and sedation, participated in the study. Informed consent was obtained. Mental function was assessed preoperatively, and at 6 and 24 hours postoperatively. Mini-Mental State (MMS) was used (1). MMS concentrates on the cognitive aspects of mental function such as orientation, registration, attention and calculation, recall and language. A retrobulbar block and intravenous sedation with fentanyl, droperidol and diazepam were given as required. The preoperative score was the control and this was compared with the scores at 6 and 24 hours. Comparison between groups was made by Students' t test for the total score and for each MMS subdivision.

Results. Our results showed a statistically significant difference between mean total scores preoperatively and at 6 hours postoperatively (Fig 1 P<.001). There was no difference between control total score and 24 hours later. There was a significant difference at 6 hours for attention and calculation (P<.05), recall (P<.02) and language (P<.001). Scores at 24 hours showed a significant difference for recall (P<.05), but no difference for orientation, registration, attention and calculation, and language (Fig 2). The range for normal cognitive function is from 24 to 30. An impaired level of cognitive function was found in 20 patients pre-op (22%), 32 at 6 hours (35.5%), and 15 at 24 hours (16.6%).

Discussion. Since 37.7% of patients had impaired cognitive function at some stage in the perioperative period, and 35.5% were impaired at one or both stages postoperatively, it seems that the increasing trend to perform cataract surgery on a day bed basis, should be encouraged only if accompanied by a screening test, such as MMS, which would allow identification and admission for further recovery, of patients with impaired cognitive function.

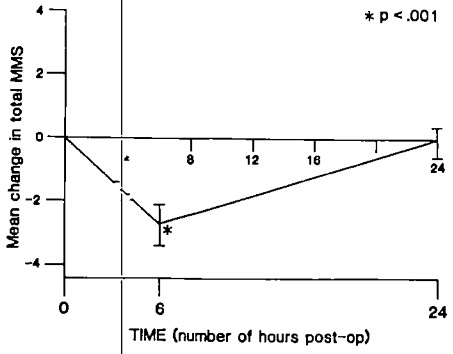

Fig. 1

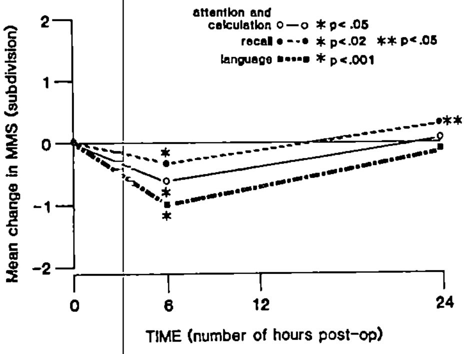

Fig. 2

References

1. Marshall F. Folstein, Susan E. Folstein, Paul R. McHugh. "Mini-Mental State" a practical method for grading the cognitive state of patients for the physician. J Psychiat Res, 1975; 12: 189-193.

Title: PaO$_2$ DURING PREOXYGENATION: THE INFLUENCE OF FACE MASK FIT, TIME AND PREOPERATIVE PULMONARY FUNCTION

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Introduction. While preoxygenation prior to anesthetic induction, laryngoscopy and endotracheal intubation increases arterial oxygenation, the influence and interaction of face mask fit (proximity of the anesthetic mask to the face), time and preoperative pulmonary function on PaO$_2$ during this interval has not been documented. Therefore, the purpose of this study was to quantitate the influence and interaction of face mask proximity (GAP); preoperative pulmonary function (as measured by FEV$_1$) and time on the rate of rise and ultimate PaO$_2$ during preoxygenation in preoperative patients.

Method. Twenty adult patients scheduled for operations requiring an arterial catheter provided informed consent and served as the experimental subjects. Each had a forced expiratory volume (FEV$_1$) performed prior to operation and were placed in Groups I and II, respectively, if FEV$_1$ was > or < 50% of predicted. All patients received diazepam, 10 mg PO, one hour prior to beginning the study and had an arterial catheter inserted into a radial artery for blood gas sampling. A No. 3 adult face mask was modified by gluing three 1x2x1 cm spacers (Lego®) to the rim so that additional spacers could be added to obtain the required GAP. A standard No. 3 adult face mask was used when the mask was applied to the patient's face. A Mapleson A circuit with a fresh gas flow of 8 L/min of oxygen was used in all cases. The circuit pop-off valve was closed when the mask was held away from the patient and fully open when the mask was on the patient's face. Preoxygenation was performed at distances of 4, 2, 1 and 0 cm from the face for 4 min. each. A 15 minute stabilization period during which the patient breathed room air was allowed between preoxygenation at each distance. Arterial samples for blood gas analysis were taken before (control), and at 1, 2, 3, and 4 minutes during preoxygenation. Correlation coefficient matrices and multiple regression equations were computed using a commercially obtained statistical processing software (1).

Results. PaO$_2$ rose fastest and attained highest values in patients with FEV$_1$ > 50% and the face mask on the face (0 GAP). The PaO$_2$ of Group I patients at 0 GAP was 283 ± 16 mmHg* by 2 mins and 317 ± 13 mmHg* at 4 min. In contrast, patients with GAPs of 4 cm and FEV$_1$ <50% the PaO$_2$ was 95 ± 7 mmHg* by 2 min and 109 ± 7 mmHg* at 4 min. While FEV$_1$, GAP and time all were correlated with PaO$_2$, the best predictor was FEV$_1$ and the least time, Table 1. When FEV$_1$ and GAP are known, PaO$_2$ can be predicted at any time from the following equation:

$$PaO_2 = B_0 + B_1 * FEV_1 + B_2 * TIME \quad \text{(Eq. 1)}$$

Correlation coefficients of the four groups are shown in Table 2 and computed regression planes in Fig. 1.

Conclusions. The results of this study demonstrate that increases of PaO$_2$ during preoxygenation are directly related to FEV$_1$, time and indirectly to mask leak. They also indicate that with large mask leaks, time and FEV$_1$ have less effect on PaO$_2$ and with no leak FEV$_1$ is the most important determinant of the rate of rise and ultimate PaO$_2$ attainable. Our data provide quantitative evidence that patients with impaired pulmonary function require minimal mask leak and increased time to maximize PaO$_2$ during preoxygenation and enable prediction of PaO$_2$ vs time at any FEV$_1$ and measured mask leak (GAP).

* Data expressed as mean ± S.E.

Table 1. Correlation of predictors with PaO$_2$

Predictor	r
FEV$_1$	0.57
GAP	-0.49
TIME	0.31

Table 2. Correlation coefficients for predictor factors of PaO$_2$· with GAP constant

GAP	FEV$_1$	TIME
0	0.7065	0.3670
1	0.7353	0.4756
2	0.7014	0.3982
4	0.5397	0.1618

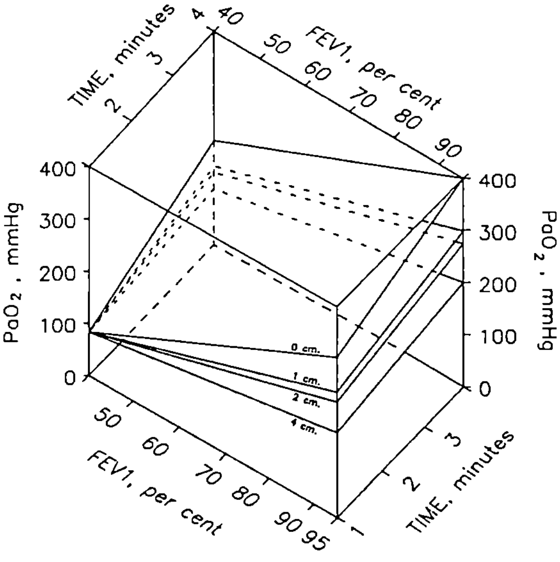

Figure 1. Regression planes for prediction of PaO$_2$

References

1. Trajectories. Version 4.0. Data Basics, Inc. Ann Arbor, Michigan. 1983

Title: MINIMIZING FRICTION IN GLASS SYRINGES FOR LOCATING THE EPIDURAL SPACE

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Introduction. The epidural space is frequently located by loss of resistance to injection of air through a glass syringe. Glass syringes are used because the glass to glass contact of the plunger and the barrel offer low resistance and allow the plunger to "bounce back" when the air is compressed. Further, this low resistance facilitates advancement of the plunger when the epidural space is reached. It is therefore desirable that the friction between the plunger and the barrel be minimized. Whereas anesthesiologists frequently lubricate the syringe with liquids in order to decrease resistance, it is our contention that dry polishing the plunger within the barrel will in fact achieve this aim. We further believe that lubricating syringes with liquids will tend to increase resistance. This study was designed to evaluate plunger resistance in glass syringes that; 1) have or have not been polished and 2) that have or have not been lubricated with saline.

Methods. New 5ml glass syringes (Deseret) were used for each experiment (n=16). Polishing of the plunger was achieved by rotating the barrel five full revolutions in both directions around the stationary plunger. Saline lubrication was accomplished by dipping the barrel and plunger into saline, thoroughly wetting both surfaces. In polished/lubricated syringes the above procedures were combined.

Four groups of syringes were studied: 1) Unpolished and dry; 2) Polished and dry; 3) Unpolished and saline lubricated; 4) Polished and saline lubricated. The barrel of the syringe was mounted in the horizontal position in a syringe pump (Sage 351) and the plunger connected to a force transducer (Grass 10D) to measure static force of resistance (fs) at the instant that movement began and dynamic force of resistance (fd). The force transducer was connected to a chart recorder (Gould 2400) for measurement of (f). The plunger was withdrawn at a rate of 6.5 cm/min. All measurements were conducted at room temperature. Data were analyzed using Student's T test for paired data. $P < 0.05$ was considered significant.

Results. In all cases, polishing of the syringe barrel against the plunger significantly reduced fs and fd. In the dry syringes, polishing reduced fs from 11.38 + 3.48(g) to 5.29 + 2.09(g) and fd from 8.16 ± 3.28(g) to 4.38 ± 0.94(g) (Table). In the saline lubricated syringes both resistance measurements (fs and fd) were significantly higher than the dry syringes. Polishing reduced fs in the saline syringes from 53.18 ± 15 to 23.5 ± 11(g) and fd from 40.9 ± 15.2 to 19.9 ± 4.2(g).

Discussion. Epidural anesthetic technique is centered around accurate and safe location of the epidural space. Loss of resistance to air is a well established method of locating this space. Because the complications of accidental dural puncture are potentially severe, it is of vital importance that problems with equipment and technique be minimized. Loss of resistance to air would be unreliable if syringe plungers were adherent to the barrel surfaces. On the other hand, syringes which have only minimal resistance to plunger motion make this technique safe and reliable. The force required to move a syringe plunger is equal in magnitude and opposite in direction to the force of resistance manifested through contact with the barrel. Our data indicate that polishing reduces resistance whether the syringes are saline lubricated, or dry. Further, our data shows that wet lubrication of the syringe consistently increases resistance to motion of the plunger. The best results (i.e., lowest resistance) were achieved with dry polishing (Table). We therefore suggest that the best way to maximize sensitivity of the "loss of resistance to air" technique, is to polish the plunger in the barrel of the syringe while keeping the glass to glass interface dry.

TABLE

FORCE OF STATIC AND DYNAMIC RESISTANCE (fs,fd)

	Unpolished Dry	Polished Dry
fs	11.38 + 3.48	5.29* + 2.09
fd	8.16 + 3.28	4.38* + 0.94
	Unpolished Saline Lubricated	Polished Saline Lubricated
fs	$53.18^{\#}$ + 15	$23.5^{*\#}$ + 11
fd	$40.9^{\#}$ + 15.2	$19.9^{*\#}$ + 4.2

* $p < 0.05$ comparing unpolished to polished
# $p < 0.05$ comparing dry to wet
fs and fd are in grams

Title: TRANSESOPHAGEAL ECHOCARDIOGRAPHY DURING LIVER TRANSPLANTATION

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Introduction. Patients with terminal liver disease undergoing liver transplantation have major hemodynamic instability intraoperatively. Cardiovascular data, obtained through the use of pulmonary artery catheters, has been described for these procedures.(1) Despite this knowledge, however, hypotension after reperfusion of the donor liver remains a problem. Hypovolemia, as well as myocardial depression have been cited as potential mechanisms of the hypotension.(2) We describe here our use of two dimensional transesophageal echocardiography (2-D TEE) during liver transplantation and its value in differentiating between hypovolemia and depression of myocardial contractility.

Method. This protocol was approved by our institutional Human Subjects Review Board. We describe two patients in whom 2-D TEE was used during liver transplantation. Anesthesia was induced with thiamylal and succinylcholine and maintained with isoflurane, oxygen/air and pancuronium. An 11 mm gastroscope tipped with a 3.5 mHz ultrasonic transducer (Diasonics, Salt Lake City, UT) was inserted into the esophagus to obtain a cross-sectional view of the left ventricle at the level of the papillary muscles. The Diasonics CardioVue 6400 Ultrasonograph was used to continuously display images. Video recordings were made of these images from which left ventricular end-systolic diameter (LVESD) and end-diastolic diameter (LVEDD) were measured; the percentage of change in diameter (%ΔD) was calculated.

The first patient was a 28-year-old female with liver failure secondary to Budd-Chiari syndrome. The liver failure was associated with intermittant coma and massive ascites. The second patient was a 56-year-old female with cirrhosis secondary to chronic active hepatitis. Echocardiograms performed in both patients several weeks prior to transplantation showed normal left ventricular function and chamber size.

Results. Initial evaluation of the 2-D TEE in patient 1 showed poor septal wall motion, as well as small LVESD and LVEDD. Initial pulmonary capillary wedge pressures (PCWP) were between 12 and 17, and cardiac outputs were 3.5 to 5 L/min. If 2-D TEE had not been used, we would have stopped volume infusion after PCWP reached 17 mmHg. However, guided by the small cavity dimensions, we infused volume, resulting in an increase in cavity dimension; PCWP increased to 20 and cardiac output to 7 L/min. Release of ascites resulted in improvement in septal wall motion and an increase in LVEDD from 3.3 cm to 4.2 cm; %ΔD improved from 18 to 33%. Subsequently, reperfusion of the donor liver was associated with a 30% decrease in blood pressure. Although fluid loading before cross-clamp release increased the LVEDD to 5.5 cm (%ΔD = 47%), LVEDD dropped after reperfusion to 2.2 cm, and %ΔD was 59%. Infusion of volume as well as calcium, glucose, and bicarbonate resulted in a return of blood pressure to baseline, an increase in PCWP to 25, and a return to normal in LVEDD.

Echocardiographic images in patient 2 were also initially associated with small LVEDD (2.8 cm), a PCWP of 9 mmHg and a cardiac output of 4-5 L/min. Infusion of volume increased LVEDD (4.2 cm), PCWP to 18, and cardiac output to 6 L/min; %ΔD was relatively unchanged (53% from 57%). Reperfusion of the donor liver was associated with a 40% decrease in blood pressure, as well as a fall in PCWP to 9 mmHg, and a decrease in LVEDD from 5.2 to 4.0 cm. This depression was alleviated by an infusion of volume and calcium; blood pressure returned to normal, PCWP increased to 10 mmHg, and cardiac output to 7.5 L/min. The %ΔD was 36% before releasing the cross-clamp, and 40% after release.

Discussion. The use of 2-D TEE was invaluable in the management of these two patients. The hypotension after reperfusion of the donor liver was seen to be largely due to hypovolemia, which was then appropriately managed with fluids. The 2-D TEE enabled us to avoid treatment with sympathomimetic drugs, which otherwise would have been used with such a high PCWP; these drugs cause vasoconstriction which can reduce splanchnic blood flow, theoretically to the point of affecting graft survival.

The hypotension after unclamping the portal vein and vena cava has been reported to be accompanied by a decrease in cardiac output even when PCWP was restored to baseline values, suggestive of myocardial dysfunction.(1) The results of our study suggest that this hypotension is largely due to decreased blood volume and not gross myocardial depression; %ΔD did not decrease after release of the cross-clamp. Hypovolemia appeared to be the major determinant of hypotension.

PCWP did not predict preload as determined by LVEDD. Patients who have undergone coronary bypass grafting show similar discrepancies.(3) These changes in compliance may be due to mechanical effects, such as right ventricular dilation, interventricular septal shift secondary to pulmonary disease and mechanical ventilation, or massive ascites. In patient 1, interventricular septal movement improved after removal of the ascites.

Two-dimensional echocardiography allows more specific diagnosis and treatment of the causes of the hypotension seen during liver transplantation, and may benefit graft, and consequently patient outcome.

References.

1. Carmichael FJ, Lindop MJ, Farman JV. Anesthesia for hepatic transplantation: cardiovascular and metabolic alterations and their management. Anesth Analg 1985; 64:108-16.
2. Joseph WL, Fonkalsrud EW, Longmire WP. Vasodepressive effects of the venous effluent following canine liver allotransplantation. J Surg Res 1968; 8:367-72.
3. Hansen RM, Viquerat CE, Matthay M et al. Poor correlation between pulmonary arterial wedge pressure and left ventricular end diastolic volume after coronary artery bypass graft surgery. Anesthesiology 1986; 64:764-70.

Title: AN IN VIVO ^{19}F NMR STUDY AT 5.6 TESLA OF HALOTHANE UPTAKE AND ELIMINATION IN ANESTHETIZED RATS

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Introduction. Fluorinated anesthetics were detected in vivo in the brains of anesthetized rats by performing nuclear magnetic resonance (NMR) spectroscopy at a higher magnetic field (5.6 Tesla) than that used in previous in vivo fluorine studies. The objectives of this study were to see: 1) if high magnetic fields make it possible to discern distinct molecular environments, or compartments, in vivo; and, 2) if NMR measurements of the uptake and elimination characteristics of general anesthetics generally agree with well established concepts of solubility (1). Recently published reports have indicated that in vivo NMR studies in rabbits demonstrate the intracranial presence of sizeable quantities of halothane (≈ 20% of the maximal detected value) some 98 hours after anesthesia is discontinued (2,3).

Methods. Five randomly chosen adult Sprague-Dawley rats (350-450 gms) were anesthetized with halothane and oxygen, paralyzed with 2 mg of pancuronium, and mechanically ventilated. Normal body temperature, (39 ± 1)°C, was maintained throughout the study. NMR measurements were performed in vivo in the prone position, using a 12x8 mm two-turn elliptical surface NMR detection coil that was placed over the head. The associated balanced matched resonance circuit for the coil was tuned to 222.77 MHz, the ^{19}F operating frequency of our 5.6 Tesla horizontal bore spectrometer. Chemical shifts were measured relative to the narrow potassium fluoride signal (0.2 ppm) in a reference capillary tube that was 5 mm away from the NMR detection coil. Spectra were determined every 4.7 minutes from 128 data acquisitions. An air flow of 10 liters/minute was maintained through the magnet bore to eliminate the sharp background signal that appears if halothane vapor is allowed to collect near the coil. NMR signal intensities were determined from the areas of Lorentzian curves that were fit to the spectra with a least-squares computerized algorithm. A special depth-pulse technique (4) was used to assure that the signals came from intracranial tissue. A modified saturation-recovery method was used to determine the spin-lattice relaxation time, T_1, to an accuracy of 10%. In all five animals we measured: the time course of halothane wash-in (wash-out) after abruptly raising (lowering) the inspired anesthetic concentration from 0.25% to 1.00% (1.00% to 0.00%); and the T_1 relaxation time. All five animals were recovered from anesthesia at the end of the experiment. Three special studies were also performed: a) in one rat a 6x4 mm coil was placed directly on the dura after a partial craniectomy; b) in one rat a coil was placed over the thigh; and, c) one rat was anesthetized with isoflurane instead of halothane.

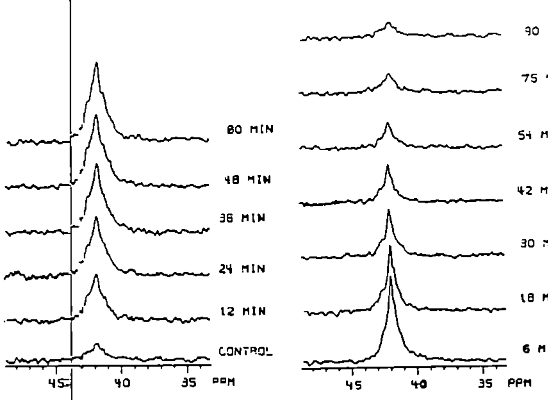
Results. With halothane, a single resonance was clearly observed with a chemical shift -42 ppm downfield from the KF reference signal. The T_1 relaxation time of this peak is -2.0 secs. Sample halothane wash-in/wash-out spectra are shown in Figure 1. In the halothane wash-out studies, the fluorine peak diminished by -60 percent within 36 minutes, and no fluorine signal was detectable in any animal 90 minutes after halothane and isoflurane anesthesia were discontinued. In the halothane wash-in studies, a steady NMR signal was achieved within -40 minutes. A smaller fluorine signal was seen at greater depths.

Discussion. The rapid NMR wash-in and wash-out measurements of halothane's cerebral intracellular fluorine signal significantly disagree with the results of recent one-pulse, surface-coil NMR studies on anesthetic wash-in and wash-out kinetics (2,3) that find -40% of the total fluorine signal to be visible 7 hours after the halothane is discontinued. Our depth-pulse studies are, however, consistent with with past and present studies that employ conventional invasive techniques.

References.

1. Eger EI. Anesthetic uptake and action. Williams and Wilkins, 1974.
2. Wyrwicz AM, Pszenny MH, Schofield JC, et al: Noninvasive observations of fluorinated anesthetics in rabbit brain by fluorine-19 nuclear magnetic resonance. Science 1983; **222**:428-430, 1983.
3. Wyrwicz AM, Pszenny MH, Nichols BG, and Tillman PC. In vivo ^{19}F NMR study of halothane and isoflurane elimination from a rabbit brain. Anesthesiology 198[illegible]; **61A**:A156.
4. González-Méndez R, Moseley ME, Murphy-Boesch J, Chew WL, Litt L, and James TL. Selective inversion with surface coils: use of depth pulses for the inversion transfer experiment in vivo. J Mag Res 1985; [illegible]5:516-521.

Figure 1.



Title: HOW MODERN ANESTHESIA MACHINES RESPOND TO DECREASES IN OXYGEN LINE PRESSURE

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Introduction. Loss of oxygen supply pressure during nitrous oxide anesthesia has caused morbidity and mortality.[1] The shift to bulk oxygen delivery systems has reduced the frequency of oxygen pressure loss; however, bulk systems can fail.[2] The ANSI standard requires that anesthesia machines be fitted with a fail-safe device to reduce or stop the delivery of other gases when oxygen supply pressure decreases by 50%.[3] We compared the fail-safe performance characteristics of several brands of anesthesia machines in daily use at our institution.

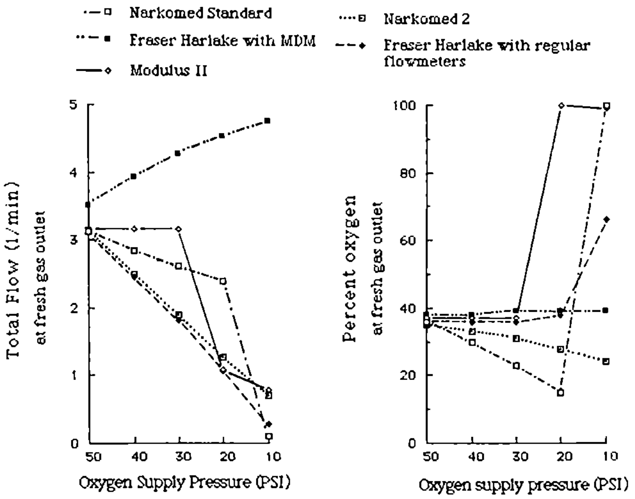
Methods. Every model anesthesia machine used in our main OR was tested: Ohmeda Modulus II (n=1), Fraser Harlake Boyle 50 with Monitored Dial Mixer (MDM) (n=3), Fraser Harlake Boyle 50 with conventional flowmeters (n=2), North American Drager (NAD) Narkomed Standard (n=3), and NAD Narkomed 2 (n=2). A variable pressure regulator equipped with a pressure gauge (Speedaire Model 2Z767A) was placed between the oxygen wall outlet and the anesthesia machine; it was initially set to 50 PSI. The flowmeters on the anesthesia machine were set to 2 L/min N_2O and 1 L/min O_2. Oxygen supply pressure was then decreased in 10 PSI increments without further adjustment of the flow needle valves. At each pressure setting, total flow and percent oxygen were measured at the fresh gas outlet. Total flow was calculated with a Collins Respirometer. Percent oxygen was measured with a calibrated Critikon OxyChek oxygen analyzer.

Results. The results for a representative machine of each model are shown in Figures 1 and 2. The machines did not allow nitrous oxide to flow when oxygen supply pressure was zero. All, except the Narkomed Standard, delivered stable oxygen concentrations down to oxygen line pressures of 30 PSI. Oxygen flow from the Narkomed Standard decreased without change in nitrous oxide flow until the nitrous oxide fail-safe valve was activated at 20 PSI of oxygen. The Narkomed 2 and the Fraser Harlake with conventional flowmeters responded with both an oxygen flow decrease and a proportional decrease in nitrous oxide flow. The Modulus II and the Fraser Harlake with MDM proportionator kept total flow and oxygen concentration stable at decreased oxygen supply pressures. Below 25 PSI oxygen the Ohio machine shut off all nitrous oxide flow; below 10 PSI oxygen the Fraser Harlake machine decreased nitrous oxide flow in proportion to the decrease in oxygen flow.

Discussion. All the machines tested are equipped with oxygen fail-safe devices which comply with the ANSI standard.[3] However, some methods of providing this safety feature worked better than others.

In a situation where there was a sudden loss of all pipeline pressure, the machines responded comparably. With moderate drops in pressure down to 25 PSI, the Modulus II and Fraser Harlake with MDM proportionator delivered both unaltered flows and stable oxygen concentrations (the MDM was stable down to 10 PSI oxygen). When the pressure of oxygen gradually fell to zero, only the Modulus II delivered the preset oxygen concentration followed by a period of 100% oxygen delivery before all flows ceased.

We feel that the NAD Narkomed Standard is a potentially dangerous machine in the event of a partial loss of oxygen pipeline pressure. It responded by delivering less than 50% of the preset oxygen concentration before a safety valve was activated. Furthermore, the machine is a hazard because it lacks an oxygen pipeline pressure gauge and a low oxygen supply pressure alarm.



References.

1. Epstein RM, Rackow H, Lee AS, Papper EM: Prevention of accidental breathing of anoxic gas mixtures during anesthesia. Anesthesiology 23:1, 1962

2. Bancroft ML, DuMoulin GC, Hedley-Whyte J: Hazards of hospital bulk oxygen delivery systems. Anesthesiology 52:504, 1980

3. Minimum performance and safety requirements for components and systems of continuous-flow anesthesia machines for human use. (ANSI Standard Z79.8-1979) American National Standards Institute, Inc. New York, 1979

Title: ANALYSIS OF THE ACCURACY OF THE ANESTHETIC RECORD

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Introduction: The anesthetic record is important not only for patient care, but also to recreate the patient's intraoperative course. Following a recent untoward intraoperative event at our institution, perusal of the anesthetic record revealed no trend to indicate the imminent physiologic collapse. We subsequently undertook a study designed to examine anesthetic record accuracy for three commonly recorded physiologic parameters: systolic and diastolic blood pressure, and heart rate.

Methods: The acquisition of the non-invasive blood pressure monitoring system, (Accutorr^R), with its data transmitter and printer, for our operating rooms allowed us to direct our trainees and staff to use the device for all cases (where invasive monitoring was not required) while affording us the opportunity to accumulate data without the chance of biasing information input onto the anesthetic record.

Data for one hundred and one cases was randomly collected over a two-week period. For each anesthetic record and Accutorr recording, ten paired data time points were selected and the systolic and diastolic blood pressures and heart rates were recorded. The paired time points were uniformly selected as follows:

Point 1: 5 minutes prior to induction of anesthesia
2: Induction of anesthesia
3: 5 minutes post-induction
4: 10 minutes post-induction
5: 15 minutes post-induction
6,7,8: were taken during the period of anesthetic maintenance. This period was divided into thirds and points 6,7, and 8 correspond to the mid-time point of the first, second and third time periods, respectively.
9: 5 minutes prior to end of case
10: end of case

Data was recorded as Accutorr reading minus anesthetic record value for each variable measured. Differences at each paired data point were compared and grouped according to the magnitude of the differences such that:

Group	Accutorr reading - anesthetic record values
-3	$\geq$ -20
-2	-10 to -20
-1	-5 to -10
0	-5 to +5
+1	+5 to +10
+2	+10 to +20
+3	$\geq$ 20

Differences seen in Group 0 were considered as acceptable errors in the recording and reading of data. The total number of occurrences in each group were determined as function of time point and occurrence per case.

Results: The results of the comparison of the data for systolic and diastolic blood pressure and heart rate is summarized in Table I. The ranges of differences between Accutorr and charted values were as follows: systolic blood pressure, -61 to +81; diastolic blood pressure, -48 to +62; and heart rate, -34 to +56.

Table I*

Group	-3	-2	-1	0	+1	+2	+3
Systolic BP (n=930)	4	6	6	55	12	9	7
Diastolic BP (n=930)	4	8	8	52	11	11	5
HR (n=927)	2	8	9	52	9	13	6

* Percentage of observation points
n=number of observations

Examination of Group +3 and -3 for each variable revealed an increased incidence of occurrences during periods around induction and near the end of the case. (Table II)

Table II*

Period	1	2-5 (av)	6-8 (av)	9-10 (av)
Systolic BP	6	60 (15)	17 (6)	20 (10)
Diastolic BP	4	51 (13)	22 (7)	11 (6)
Heart Rate	7	49 (12)	7 (2)	18 (9)

* number of occurrences

Groups +3 and -3 differences occurred in at least one of the parameters measured in 85 of the 101 cases (84%), with an average occurrence of 2.3 per case. The distribution of these occurrences is shown in Table III.

Table III*

Occurrences	7	6	5	4	3	2	1	0
Cases	1	1	3	12	18	20	30	16

* Number of Groups +3 and -3 occurrences per case

Discussion: Significant discrepancies were discovered between the anesthetic record and the Accutorr recordings. The magnitude of these differences were unexpected, although the times of their occurrence were not. Induction and emergence represent periods of time when the physician's concentration and efforts are and should be directed totally toward patient care. However, if accuracy in recording is a desirable goal, then alternative methods of generating the anesthetic record must be considered. We believe this data supports the idea of a computer-generated record not only for accuracy, but also to free the anesthesiologist from time-consuming record keeping so he can concentrate completely on patient care.

Title: ONSET OF NEUROMUSCULAR BLOCKADE WITH PANCURONIUM IN CHILDREN WITH CYANOTIC AND ACYANOTIC DISEASE

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Introduction: The speed of onset of intravenous drugs depends on the category of heart lesions: cyanotic (predominant right-to-left shunt) > normal > acyanotic (predominant left-to-right shunt). However, Maunuksela et al[1] found no difference in either dose requirements of pancuronium or the time of onset of neuromuscular blockade between children with cyanotic and acyanotic CHD. Because they assessed the neuromuscular blockade subjectively, we designed a study to assess the neuromuscular blockade in a quantitative fashion. We compared both the time to 95% twitch depression and the intubating conditions in children with CHD who were paralyzed with pancuronium.

Methods: With approval from our Human Research Committee, 33 children with cyanotic or acyanotic CHD ages 2-8 years were studied. The children were all ASA III, fasting, and premedicated with pentobarbital 2 mg/kg, morphine 0.2 mg/kg, and atropine 0.02 mg/kg. Children were excluded from this study if there was evidence of neuromuscular or renal disease, or if a difficult intubation was anticipated. Pre-induction monitoring included an EKG, precordial stethoscope, BP cuff, doppler, and pulse oximeter. Anesthesia was induced with intravenous ketamine 1-3 mg/kg and fentanyl 1-3 µg/kg. Anesthesia was maintained with supplemental doses of ketamine and fentanyl as necessary and nitrous oxide in oxygen by face mask. Ventilation was spontaneous.

The ulnar nerve was stimulated at the wrist using supramaximal squares waves of 0.2 msec duration at a frequency of 0.15 Hz. The stimuli were delivered by a Grass S4 nerve stimulator through an SIU5 isolation unit. The force of thumb adduction was measured using a Grass FT03 force transducer and recorded on a Gould #2200S recorder. After a stable twitch response was obtained, each child was paralyzed with a rapid intravenous injection of pancuronium 0.15 mg/kg. When the twitch was depressed 95%, the trachea was intubated. The intubating conditions were assessed according to the criteria of Lund and Stovner.[2] The results of this study were compared to the results from a similar group of children without CHD (control) who were anesthetized with intravenous thiopental 5 mg/kg, atropine 0.02 mg/kg and pancuronium 0.15 mg/kg followed by nitrous oxide (70%) and oxygen (30%).[3] Statistical significance ($p < 0.05$) was determined using analysis of variance, the Student-Newman-Keuls test, and the Fisher exact test.

Results: There was no significant difference in age or weight among the three groups (Table). Hemoglobin was significantly greater in the cyanotic group compared to the other two groups. The time to 95% twitch depression was not significantly different in the cyanotic and acyanotic groups, however the times for both CHD groups were significantly longer than that in the control group (Table). The intubating conditions were excellent in all patients studied.

Discussion: Current teaching states that the speed of onset of intravenous drugs is more rapid in patients with cyanotic heart disease, and slower in patients with acyanotic heart disease than in normal patients. Our results do not support this teaching. The delayed onset of neuromuscular blockade in cyanotic children may be attributed in part, to an increased volume of distribution, increased protein binding, and decreased muscle blood flow. The delayed onset of action in acyanotic children may be attributed in part, to the recirculation of pancuronium through the pulmonary circulation. We conclude that the time to 95% twitch depression with pancuronium 0.15 mg/kg in children with CHD exceeds that which one would expect in normal children by 50-75%.

References:
1. Maunuksela E, Gattiker RI. Use of pancuronium in children with congenital heart disease. Anesth Analg 1981;60:798-801
2. Lund I, Stovner J. Dose response curves for tubocurare, alcuronium and pancuronium. Acta Anaesthesiol Scand 1970;37:238-42
3. Cunliffe M, Lerman J, McLeod ME, Burrows FA. Neuromuscular blockade for rapid intubation in children: pancuronium is slower than succinylcholine. Anesthesiology 1985;63(3A):A474

Table

Groups	Cyanotic	Acyanotic	Control[3]
No. of patients	14	19	11
Time to 95% twitch depression (sec)	138.6 ± 49.3	118.7 ± 31.3	79.9* ± 22.2
Age (years)	4.2 ± 2.1	4.7 ± 1.5	4.1 ± 2.0
Weight (kg)	14.6 ± 3.6	16.7 ± 4.1	17.9 ± 4.1
Hemoglobin (gm%)	171* ± 21	125 ± 10	124 ± 5

Data are Mean ± S.D.
* $p < 0.01$ compared to the other groups

Title: ULTRASONIC NEBULIZATION OF LIDOCAINE: SAFETY AND EFFICACY

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Introduction: Ultrasonic nebulizers have been advocated for administration of topical lidocaine to achieve oropharyngeal, laryngeal, and tracheobronchial anesthesia and for chronic cough suppression.[1,2] The total dose of lidocaine in most studies is excessive if absorption from the oropharynx is as rapid as has been reported.[3,4] Our clinical experience demonstrated that a volume of 15 ml of lidocaine was necessary to achieve effective anesthesia consistently. Using this volume, we encountered no clinical signs of local anesthetic toxicity. The purpose of this study was to determine blood lidocaine levels that resulted from the administration of 15 ml of 4% lidocaine by ultrasonic nebulization using two modes of administration.

Materials and Methods: Twelve patients scheduled to undergo bronchoscopy or awake nasotracheal intubation were selected for the study. The study was approved by the Medical Research Committee and informed consent obtained. Patients age ranged between 14 and 65 years and weight ranged between 40 and 100 kgs. All patients were ASA status 1 or 2. Patients were divided into two groups of six patients each. Patients received 15 ml of 4% solution of lidocaine delivered by a standard ultrasonic nebulizer either via an aerosol mask (Group 1) or via a mouthpiece without a noseclip (Group II) Administration was complete in 10-15 minutes. Venous blood samples were collected from an indewelling catheter. Blood samples were collected at 2, 4, 6 and 15 minutes after completing the aerosol administration. The serum drug levels were analyzed by florescent polarization method using the Abbott TDX® analyzer.[5,6]

Results: The serum levels of lidocaine in the two groups are shown in figures 1 and 2. One patient weighing 42 kg in Group I had serum levels of lidocaine at the upper limit of the therapeutic range. One patient weighing 71 kg in Group II had a serum level of lidocaine in the toxic range (> 5.0 μg/ml) at four minutes, but showed no clinical signs of toxicity. Peak lidocaine levels in all patients occurred at 2-6 minutes after completion of ultrasonic nebulization. All patients had subjective numbness of the oropharynx and underwent either a bronchoscopy or awake nasotracheal intubation with light sedation, but without additional lidocaine.

Discussion: Although anesthesia of the oropharynx, larynx and tracheobronchial tree can be achieved by direct spray and transtracheal block, the use of an ultrasonic nebulizer to administer the local anesthetic is more convenient and more comfortable for the patient. Also, transtracheal block is contraindicated in the presence of clotting abnormalities or an enlarged thyroid, and direct topical spray is impossible for a patient whose jaw is wired or who cannot open his mouth for other reasons (pain, infection, etc.) When lidocaine is administered via an aerosol mask, an undetermined amount of drug escapes into the atmosphere. When the drug is administered via a mouthpiece, a lesser amount of drug escapes and potentially more drug is absorbed. The one patient who attained a transient blood level greater than 5 μg/ml was in the group that used a mouthpiece.

Ultrasonic nebulization of lidocaine is a comfortable, safe and effective way to achieve oropharyngeal, laryngeal, and tracheobronchial anesthesia. It should be noted, however, that occasionally a patient may attain blood levels of lidocaine that approach the toxic range.

REFERENCES:

1. Christoforidis AJ, Tomashefski JF, Mitchell RI: Use of an ultrasonic nebulizer for the application of oropharyngeal, laryngeal and tracheobronchial anesthesia. Chest 59:629-633, 1971.
2. Sanders RV, Kirkpatrick MB: Prolonged suppression of cough after inhalation of lidocaine in a patient with sarcoid. JAMA 252:2456-2457, 1984.
3. Chinn WM, Zavala DC, Ambre J: Plasma levels of lidocaine following nebulized aerosol administration. Chest 71:346-347, 1977.
4. Pelton DA, Daly M, Cooper PD, et al: Plasma lidocaine concentrations following topical aerosol application to the trachea and bronchi. Can Anaesth Soc J 17:250-255, 1970.
5. Koch-Weser J: Correlation of serum concentrations and pharmacologic effects of antiarrhythmic drugs. Proceeding 5th international congress pharmacology 3:59-85, 1972.
6. Bromage PR, Robson JG: Concentrations of lidocaine in the blood after intravenous, intramuscular, epidural and endotracheal administration. Anesthesia 16 461-478, 1961.

Lidocaine via mask (group I)

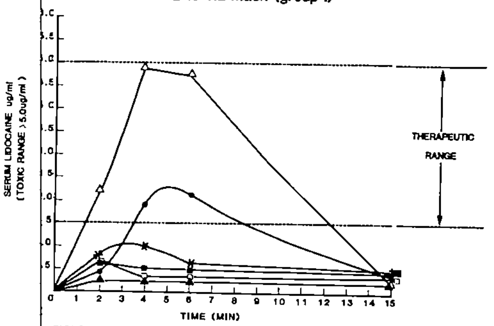

FIGURE I - SEQUENTIAL CHANGES OF BLOOD LIDOCAINE WITH TIME

Lidocaine via mouthpiece (group II)

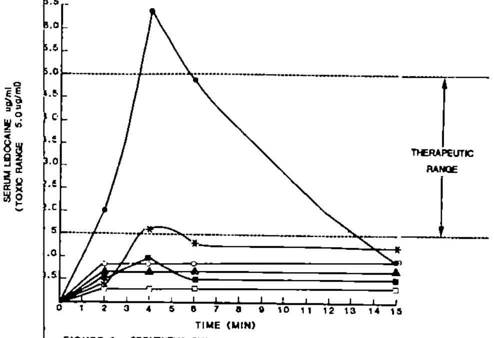

FIGURE 2 SEQUENTIAL CHANGES OF BLOOD LIDOCAINE WITH TIME

Title: CAN AMRINONE REVERSE VERAPAMIL-PROPRANOLOL INDUCED CARDIAC DEPRESSION DURING ISOFLURANE ANESTHESIA IN DOGS?

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Introduction. The problem of combined myocardial depression with verapamil (V) and propranolol (P) is a difficult one to treat because of the severe combined effects on the slow calcium channel (1,2). Amrinone (A) acts distal to the beta receptor to increase intracellular cyclic AMP and results in an increase of slow calcium channel function. This study was designed to investigate the possibility of whether V mitigates the effects of A, whether A can reverse VP depression, and also to evaluate, whether the order of administering the drugs would have any effect.

Methods. At 3-4 week intervals, each of 6 conditioned mongrel dogs (23±1 kg) received A, V and P in 4 different orders of administration: VAP, AVP, VPA, and PVA. The dogs were anesthetized with 1.7-1.8 % end tidal isoflurane (F). Normocarbia and normothermia were maintained. The end tidal concentrations of F, O_2, and CO_2 were continuously measured by mass spectrometry. Arterial and pulmonary arterial catheters were placed for blood sampling, mean arterial, central venous and pulmonary capillary wedge pressure (MAP, CVP, PCWP) measurements, and for determination of cardiac output. A micromanometer-tipped catheter was placed for direct left ventricular (LV) pressure measurements and electronic derivation of LV dP/dt. Systemic and pulmonary vascular resistances, cardiac index, stroke volume index, and stroke work index (SVR, PVR, CI, SVI, SWI) were calculated. Periodic blood samples were analyzed for epinephrine, norepinephrine (EPI, NEPI), A, V and P by HPLC. After 60 min of stabilization on the anesthetic, baseline cardiovascular measurements and blood samples were taken. Group VAP received a bolus of V followed by a constant 30-min infusion (200 ug/kg + 7.5 ug/kg/min); then A bolus and infusion (4mg/kg + 100 ug/kg/min) were added to V infusion for 30 min, and finally P bolus and infusion (150 ug/kg + 0.8 ug/kg/min) were added, and all 3 drugs were infused together for 60 min. In groups AVP, VPA, and PVA the bolus doses and infusion rates of the drugs were the same as for group VAP. Measurements and blood samples were repeated at 30 min of each drug administration period and also at recovery, 30 and 60 min after cessation of drug infusions. Analysis of variance and analysis of variance for repeated measures with Bonferroni modified t-tests were used for statistical analysis. $P < 0.05$ was considered statistically significant.

Results. There were no differences in any variable at the time of baseline measurements among groups VAP, AVP, VPA and PVA. The end tidal F concentrations were stable over time in each group and equivalent among the groups. Baseline and successive 30 min values for HR, PR interval, MAP, LV dP/dt, CI, and SVR are given in the table. V alone (~100 ng/ml in VAP and VPA) caused an increase in PR interval and decrease in MAP, LV dP/dt and SWI; in addition, in VPA, V also increased CVP. The addition of P (~33 ng/ml) to V or V to P (VPA, PVA) caused a marked cardiac depression (60 min in table) with increased catecholamine levels after PV in PVA, and in 4/6 animals after VP in VPA. Adding A, at plasma levels of ~18 ug/ml, to V improved cardiac function and caused systemic and pulmonary vasodilation without any increase in catecholamines, but MAP remained low (VAP, 60 min). When V was added to A (in AVP), PR, SVI and CVP increased with decreased MAP when compared to A alone. The addition of A to VP and PV improved cardiac function more in PVA than in VPA (90 min) without increase in catecholamines in either group. There were no differences between groups at 90 min with all 3 drugs present except for LV dP/dt (VPA < AVP) and SVR (VPA > VAP). At recovery (180 min=R), 60 min after cessation of drug infusions, the only difference among groups was in LV dP/dt (VPA < AVP).

Discussion. The results of this study showed that A was able to reverse many of the effects of V (VAP) and also many of the effects of VP or PV (VPA, PVA), combinations which may significantly diminish hepatic clearance of both drugs, and may cause severe cardiovascular consequences (1,2). However, MAP remained low. Consistent with a previous study (3), A did not cause any increase in plasma catecholamines while it improved cardiac performance. Thus we have shown that A is of therapeutic value not only for disease induced myocardial depression but also for the reversal of untoward effects of pharmacologic interventions with potent cardiodepressant drugs such as V and P, even in the presence of inhalation anesthetics.

References.

1. Sullivan K, Kapur P. The effect of beta-adrenergic blockade on the cardiovascular response to diltiazem or verapamil in dogs. Anesth Analg 1986. (In Press)
2. Hamann SR et al. Cardiovascular and pharmacokinetic consequences of combined administration of verapamil and propranolol in dogs. Am J Cardiol 1985;56:147-56.
3. Makela VHM, Kapur PA. Dose-related cardiovascular effects of amrinone during enflurane anesthesia in the dog. Anesth Analg 1986;65:849-52.

Table. Cardiovascular values for verapamil-amrinone-propranolol (VAP), amrinone-verapamil-propranolol (AVP), verapamil-propranolol-amrinone (VPA), and propranolol-verapamil-amrinone (PVA) groups.

Time (min)		0=C	30		60		90		180=R
HR (bpm)	VAP	126±6	122±5	V	131±6	VA	115±8	VAP*	110±8
	AVP	131±4	152±7	A	141±7	AV	124±9	AVP	111±7
	VPA	128±9	121±7	V	96±10	VP*	109±9	VPA	105±8
	PVA	122±9	119±9	P	109±8	PV	116±9	PVA	113±4
PR (msec)	VAP	117± 6	153±10	V*	135±10	VA	151±15	VAP	123±5
	AVP	118± 4	101± 2	A*	131± 8	AV*	152±13	AVP	128±7
	VPA	113±10	153± 8	V*	197±12	VP*	161±16	VPA*	130±6
	PVA	125±10	122± 6	P	162±10	PV*	137±13	PVA	121±4
MAP (mmHg)	VAP	90±6	72±2	V*	58±2	VA*	60±3	VAP	86±4
	AVP	93±2	75±3	A	65±4	AV*	66±3	AVP	86±2
	VPA	93±6	77±4	V*	69±8	VP	65±4	VPA	85±3
	PVA	93±4	92±5	P	82±5	PV	73±3	PVA	94±5
LV dP/dt ($mmHg \cdot s^{-1}$)	VAP	2442±128	1817±193	V*	3433±297	VA*	2350±206	VAP	2483±138
	AVP	2529±174	4467±686	A	4217±543	AV	2638±209	AVP	2571±193
	VPA	2447± 86	1834±195	V*	982± 70	VP*	1801±163	VPA*	1916± 95
	PVA	2457±221	2054±116	P	1190± 75	PV*	2145±207	PVA*	2202±124
CI ($l \cdot min^{-1} \cdot m^{-2}$)	VAP	5.6±0.6	4.7±0.4	V	6.9±0.7	VA*	4.9±0.4	VAP	4.2±0.5
	AVP	5.3±0.6	6.1±1.0	A	6.8±0.7	AV	4.9±0.7	AVP	3.9±0.5
	VPA	5.3±0.6	4.4±0.5	V	1.9±0.3	VP*	3.3±0.4	VPA*	2.9±0.4
	PVA	5.4±0.6	4.2±0.3	P	2.7±0.3	PV*	3.7±0.3	PVA	3.4±0.5
SVR ($dynes \cdot s \cdot cm^{-5}$)	VAP	1442±189	1352±162	V	751± 88	VA*	1045± 95	VAP	1966±347
	AVP	1605±176	1166±138	A	830± 74	AV	1227±154	AVP	2035±258
	VPA	1595±228	1556±215	V	2960±278	VP*	1702±175	VPA*	2672±346
	PVA	1577±173	1949±129	P	2575±148	PV	1728± 90	PVA	2627±293

Mean ± SEM
* $p < 0.05$ compared to previous value for that same group.

TITLE: DO CALCIUM CHANNEL BLOCKERS ALTER VASCULAR RESPONSIVENESS?

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INTRODUCTION: Patients (pts.) undergoing coronary bypass surgery (CABG) frequently receive chronic calcium channel blocker (CCB) therapy. These antianginal agents are potent arterial smooth muscle relaxants and hypotension can occur during anesthesia induction. The hypotension could result from CCB induced α adrenergic inhibition. We utilized a phenylephrine (Phe) challenge to test the hypothesis that preoperative CCB therapy decreases the vascular responsiveness to α agonists before and during CABG. METHODS: After approval by the IRB and informed consent, 16 nonhypertensive pts. with normal left ventricular function scheduled for elective CABG were studied. Pts. were grouped on the basis of no CCB (n=4), nifedipine (n=6), or diltiazem (n=6) therapy. All were premedicated with diazepam 0.1 mg/kg, morphine 0.1 mg/kg, and scopolamine 0.2-0.4 mg and received their usual β-blockers and CCB's one hour preoperatively. Radial arterial and pulmonary artery catheters were inserted. Blood was sampled for plasma norepinephrine (NE) and epinephrine (Epi). Following baseline hemodynamic measurements a pre-induction Phe infusion was administered at incrementally increasing doses (0.1, 0.5, 1.0, 2.5, 5.0 μg/kg/min) for 5 min each until a 30% increase in mean arterial pressure (MAP) was obtained. At the end of each incremental dose, hemodynamic parameters were measured and systemic vascular resistance (SVR) was calculated. Anesthesia was then induced with fentanyl 30 μg/kg plus 0.3 μg/kg/min and pancuronium 0.1 mg/kg. During constant flow hypothermic cardiopulmonary bypass (CPB) and aortic cross clamping (AXC) a second Phe challenge was performed. Additional hemodynamic measurements were taken 5 min after induction, 10 min after sternotomy, at onset of CPB, after termination of CPB, and at chest closure. The log-linear regression for best fit of SVR versus Phe dose was determined and the Phe dose required to increase SVR 30% (ED30) was extrapolated. Comparison between preinduction and CPB ED30 and plasma catecholamines were analyzed for statistical significance with Student's t-tests. All intergroup comparisons were made by one-way ANOVA. RESULTS: Intergroup comparisons for slope (SVR/ log-dose Phe) and ED30 were not statistically different among groups during either the preinduction (Fig. 1) or CPB challenge tests. The hemodynamic function measured throughout anesthesia, surgery, and CPB was also not significantly different among groups.(Fig. 2) In all groups the decrease from baseline in SVR at the onset and termination of CPB was significant (p<0.05). Since between groups values were the same, data from all pts. were pooled for comparisons between pre-induction and CPB Phe challenge tests. The ED30 was significantly lower during CPB (p <0.05) however the slope was unchanged. Plasma NE and Epi were increased during CPB: pre-induction NE 233 ± 147 ng/ml; Epi 223 ± 50 ng/ml vs CPB NE 628 ± 462; Epi 568 ± 348. DISCUSSION: Preoperative CCB therapy did not influence hemodynamic function or the vascular responsiveness to an α_1 agonist. Therefore, there appears to be no justification for discontinuing CCB therapy prior to surgery based on concerns for vascular hyporesponsiveness. The leftward shift in the log-dose response curve during CPB without a change in slope suggests the presence of additional α agonists at the receptor site or an increase in the sensitivity to Phe. This could be due to an increase in plasma catecholamines as were demonstrated in this study. In conclusion, patients maintained on CCB will respond normally to α agonists and are even hyperresponsive during hypothermic CPB. Should hypotension occur in CCB treated patients, phenylephrine will increase the blood pressure.

Fig. 1

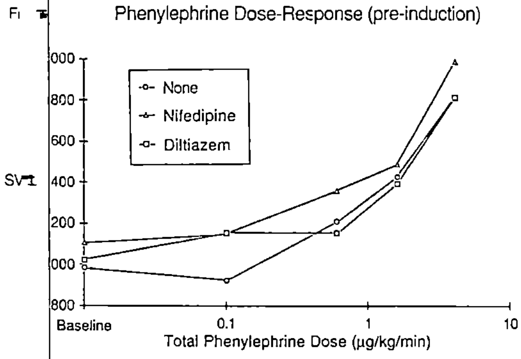
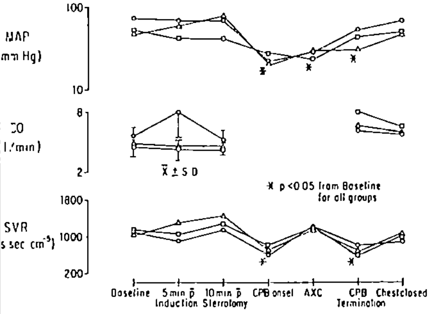


Fig. 2



Title: EPIDURAL HYDROMORPHONE VERSUS EPIDURAL MORPHINE
FOR POSTCESAREAN SECTION ANALGESIA

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Introduction: Epidural narcotics are well established as effective treatment for postcesarean section pain.(1) Morphine is the most commonly used narcotic and has been extensively studied. Hydromorphone may be a superior agent as it has a long duration of action and may have a lower incidence of side effects.

We performed a randomized, double-blind study to compare the efficacy of epidural morphine(5mg) versus epidural hydromorphone(1mg) for postcesarean section analgesia. Duration of action, subjective quality of analgesia, total narcotic dose in the first 24 hours, and incidence of side effects were evaluated.

Methods: Forty ASA I or II patients scheduled for elective cesarean section under lumbar epidural anesthesia were studied. Institutional approval was granted and written informed consent was obtained from each patient.

Preoperatively, each patient was familiarized with a 10cm visual analogue pain scale. Lumbar epidural anesthesia for cesarean section was produced using 0.5% bupivicaine, supplemented if necessary with 5cc 3% 2-chloroprocaine, to achieve a T3-T4 sensory level. No supplemental parenteral narcotics were given during surgery. The epidural narcotic was injected during fascial closure in a randomized, double-blind fashion. The morphine group, 20 patients, received morphine 5mg in 10cc (Duramorph). The hydromorphone group, 20 patients, received preservative free hydromorphone 1mg in 10cc saline.

Each patient was informed that additional intramuscular pain medication could be obtained on demand from their nurse (hydromorphone 1-2mg) every three hours. Vital signs and level of consciousness were assessed every 30 minutes for the first 8 hours, then hourly for the next 4 hours. The intensity of pain was assessed hourly for 12 hours by the patient using a 10cm visual analogue pain scale. The time until administration of the first additional pain medication, total narcotic dose in the first 24 hours, and time of first ambulation were recorded for each patient. The incidence and treatment of side effects, including pruritus, nausea and vomiting, excessive sedation, and respiratory depression were also recorded.

Statistical analysis was by non-paired Student's t-test, Fisher's exact test, and Mann-Whitney U-test as indicated by the data. Hourly pain intensity data were analyzed with a 2 factor ANOVA with repeated measures on one variable; post hoc testing was done with paired t-tests with Bonferroni's correction for multiple applications. Criterion for rejection of the null hypothesis was $p<0.05$.

Results: The results are summarized in Table 1. There was no difference between groups in age, height, weight, or time to first ambulation. There was no clinically significant respiratory depression or depression of consciousness in either group. The morphine group had a longer duration of analgesia and required less supplemental IM narcotics than the hydromorphone group. The incidence of pruritus was similar for both groups. Nausea and vomiting occurred more frequently in the morphine group, but did not reach statistical significance. Analysis of pain intensity data revealed no difference between groups at any time.

Discussion: This study demonstrates that epidural morphine provides longer lasting postcesarean section analgesia than epidural hydromorphone. The quality of pain relief provided by epidural hydromorphone was similar to that provided by epidural morphine. Although nausea and vomiting occurred more frequently with morphine, there was no difference in side effects demonstrated in this study of 40 patients. Epidural hydromorphone is effective for postcesarean section analgesia, but epidural morphine has a longer duration.

References: 1. Cousins MJ, Mather LE: Intrathecal and epidural administration of opiods. Anesthesiology 1984;61:276-310.

TABLE 1

	Morphine	Hydromorphone
Time to first supplemental analgesia (min)	1267.0 * (SD 809.4)	721.3 (SD 356.1)
Total supplemental IM hydromorphone in 24 hours (mg)	2.4 * (SD 2.4)	5.0 (SD 2.4)
Time to first ambulation (min)	708.3 (SD 251.0)	661.0 (SD 152.4)
Nausea	8/20	6/20
Nausea and vomiting	7/20	2/20
Nausea and vomiting requiring treatment	6/20	1/20
Pruritus	17/20	17/20
Pruritus requiring treatment	8/20	6/20

* morphine group different than hydromorphone group, $p< 0.05$.

Title: LACTATE EXTRACTION AND MYOCARDIAL DAMAGE FOLLOWING COUNTERSHOCK AT DIFFERENT ENERGY LEVELS

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INTRODUCTION: Anaerobic metabolism occurs in the heart after direct electric countershock (CS). Visible myocardial lesions under the area of paddle placement also occur. We studied the variation of lactate extraction and myocardial damage after CS with different energy levels.

METHODS: Twelve nongrel dogs were anesthetized with halothane in O_2 by mask. The trachea was intubated and ventilation was controlled to achieve normocarbia. End tidal halothane 1.25% to 1.5% was used. After cannulation of both femoral arteries a right thoracotomy was performed in the fourth intercostal space and the coronary sinus was cannulated via the right atrium. Heparin 1000 units and lidocaine 1.5 mg/kg were given IV. Direct CS of 5, 10, or 20 joules were delivered twice at a one minute interval to the heart using 5 cm paddles over the right and left ventricular free walls. Blood samples for the measurement of lactate extraction were obtained from the coronary sinus and the fenoral artery prior to countershock at 30 sec. after each CS, and then 1.5 min., 3.5 min., 5.5 min., 10.5 min., and 30.5 min., after the second CS. The dog was maintained under anesthesia for four hours when 10-13 mCi of technetium^{99m}pyrophosphate (Tc-PYP) was injected for uptake into damaged areas. One hour later the heart was removed and the ventricles dissected into samples containing visible lesions, border zones of lesions, and normal tissue. The radioactivity of each sample was then measured in a scintillation counter. Each sample's uptake of Tc-PYP was expressed as a sample to normal ratio (SNR) by dividing by the average activity of the septum in each heart. Plasma lactate levels were determined in duplicate using the YSI 23L lactate analyzer. Maximum reduction in lactate extraction was found by taking the difference in absolute extraciton values between baseline and each blood sample. Damage index (DI) was defined as mass weighted average specific activity for samples with SNR>3 x total weight of samples with SNR>3. Differences between groups were assessed using one way ANOVA followed by the one-tailed Student's t-test with Bonferroni correction. Statistical significance was considered at $p<0.05$.

RESULTS: As shown in Fig. 1 lactate extraction progressively decreased with increasing energy dose. Myocardial damage index (DI) also increased with increase in energy level. The nadir in lactate extraction occurred at 2.5 min., a finding consistent with earlier results.[1] Supraventricular as well as ventricular tachycardias were observed immediately after countershock in several dogs at the highest energy level, but all dogs were hemodynamically stable during the four hour period following CS.

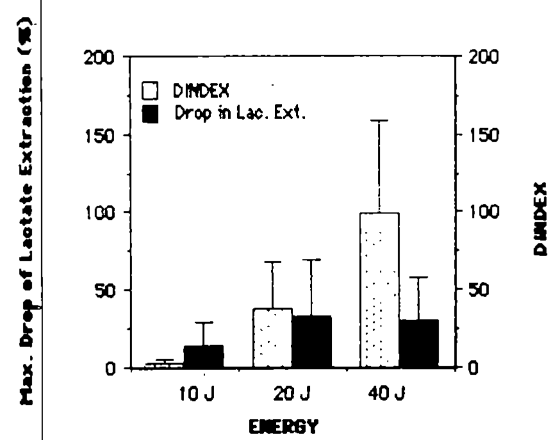
DISCUSSION: These results show that net myocardial lactate extraction as an indicator of myocardial metabolic state decreased with increasing energy levels. Prior work has shown that direct CS with high energy causes a conversion from net lactate extraction to net lactate production.[1] Normally the heart is a net lactate extractor (indicating aerobic metabolism), but during times of anaerobic metabolism the heart becomes a net lactate producer. This is important clinically because during reperfusion on CPB the heart has been shown to be a net lactate producer[2] and further insult may sufficiently alter the aerobic/anaerobic balance to result in additional compromise. The cause of post-CS myocardial necrotic lesions remains yet to be found.

REFERENCES:

1. Gaba DM, MD, Merlone S, MD, Smith C, M.Sc.: Global Myocardial Metabolism after Internal Countershock in Anesthetized Dogs. Anesthesiology A:36, 1985.

2. Reves JG, Buttner E. Larp RB, et.al: Elevated catecholamines during cardiac surgery: Consequences of reperfusion of the arrested heart. Am. J. Cardiology 53:722-728, 1984.

Figure 1



TITLE: ATRIAL NATRIURETIC PEPTIDE AND CARDIAC FUNCTION FOLLOWING CARDIAC SURGERY

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INTRODUCTION: Atrial natriuretic peptide (ANP) is a potent short-acting cardiac hormone, that reduces blood pressure by a direct effect on vascular smooth muscle[1]. Vasodilator therapy is important in the treatment of low cardiac output and vasoconstriction following cardiopulmonary bypass (CPB)[2]. We therefore examined the relationship between ANP and cardiac function during this period.

METHODS: After institutional approval and informed consent, 7 patients undergoing cardiac surgery for coronary revascularization (CABG) were studied. The mean ejection fraction was 0.51 ± 0.05 (range 0.32 - 0.68). Anesthesia was accomplished with narcotics, fentanyl or sufentanyl, supplemented by either halothane or enflurane and muscle relaxation with pancuronium. The mean duration of CPB was 156 min (74-330 min) and aortic cross-clamp time was 72 min (36-150 min). Cold potassium cardioplegia was used for myocardial protection. Arterial blood samples were withdrawn and hemodynamic variables measured at baseline (prior to induction), at the end of CPB, 5 mins following CPB, at closure of sternotomy and 2 hrs following CPB. Plasma ANP was measured by radioimmunoassay. Post-CPB treatment was not altered in any way; all patients received volume loading and 3 patients were administered sodium nitroprusside infusions (0.5 - 2.0 mcg. $min^{-1}.kg^{-1}$). Data were compared by t-tests and analysis of variance, $p<0.05$ for significance.

RESULTS: Preoperative ANP was 37 ± 8 $pg.ml^{-1}$ (mean ± SEM). Normal ANP, measured in healthy volunteers in our laboratory, is 12 ± 5 $pg.ml^{-1}$. ANP decreased following CABG and CPB (fig 1). Hemodynamic changes post-CPB are shown in table 1. There was an increase in heart rate and systemic vascular resistance and a decrease in cardiac index.

DISCUSSION: ANP is elevated in patients with heart failure and this correlates with the severity of failure[3]. The high preoperative level of ANP in our patients may therefore reflect the moderate reduction in ejection fraction. The decreasing level of ANP that we observed in the post-CPB period was accompanied by cardiac dysfunction. This was manifest by a decrease in cardiac index in spite of volume-loading and an increase in heart-rate. This finding is in agreement with other reports and is probably due to post-CPB recovery of myocardial metabolic function[4]. The decreasing level of ANP post-CPB is likely related to hypothermia and atrial ischemia during CPB. Postoperative vasoconstriction may be due in part to the declining vasodilator effect of ANP. In conclusion, ANP is ten-fold higher than normal at the end of CPB and subsequently decreases toward normal postoperatively. This has important implications for the recovery of myocardial function following anesthesia and surgery.

Figure 1

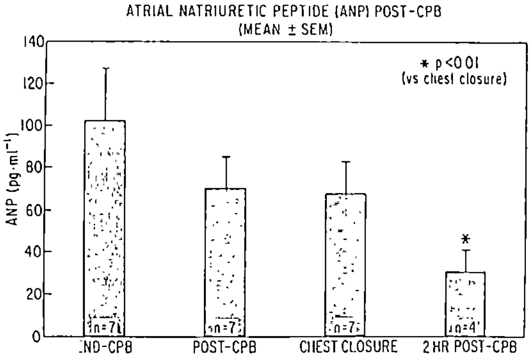

Table 1

	POST-CPB	CHEST CLOSURE	2 HR. POST-CPB
HR	89 ± 3	95 ± 6*	99 ± 6*
MAF	68 ± 5	72 ± 5	79 ± 5
RAF	9 ± 2	11 ± 5	12 ± 5
PAF	13 ± 2	15 ± 2	15 ± 3
CI	3.7 ± 0.9	3.0 ± 1.0*	2.9 ± 1.0*
SVF	18 ± 6	23 ± 10*	24 ± 8*

Mean ± SD
*$p<0.05$ vs. post-CPB

HR=heart rate (min^{-1})
MAP=mean systemic pressure (mmHg)
RAP=right atrial pressure (mmHg)
PAP=pulmonary artery diastolic pressure (mmHg)
CI=cardiac index ($l.min^{-1}.m^{-2}$)
SVR=systemic vascular resistance ($mmHg.l^{-1}.min^{-1}.m^{-2}$)

REFERENCES

1. Currie MG, Geller DM, Cole BR, Boyland JG, Yusheng W, Holmbery SW, Needleman P: Bioactive cardiac substances: Potent vasorelaxant activities in mammalian atria. Science 221:71-73, 1983.
2. Stinson EB, Holloway EL, Derby G, Oyer PE, Hollingsworth J, Griepp RB, Harrison DC: Comparative hemodynamic responses to chlorpromazine, nitroprusside, nitroglycerin, and trimethaphan immediately after open-heart operations. Circulation 51:I-26 - I-33, 1975.
3. Burrett JC, Kao PC, Hu DC, Heser DW, Heublein D, Granger JP, Reeder GS: Atrial natriuretic peptide elevation in congestive heart failure in the human. Science 231:1145-1147, 1986.
4. Fremes SE, Weisel RD, Mickle DAG, Ivanov J, Madonik MM, Seawright SJ, Houle S, McLaughlin PR, Baird RJ: Myocardial metabolism and ventricular function following cold potassium cardioplegia. J Thorac Cardiovasc Surg 89:531-546, 1985.

Title: NALBUPHINE DOES NOT EXERT AGONIST, BUT ONLY OPIATE ANTAGONIST ACTION IN AWAKE DOGS

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Introduction:

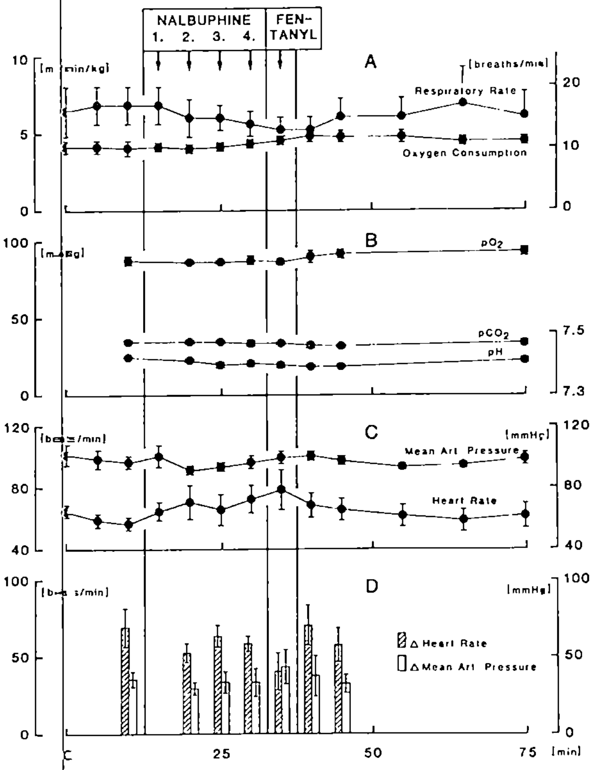
Nalbuphine is said to have opiate agonist/antagonist actions as it reverses the respiratory depressant effects of opiates while it adds to and extends the analgesic action in man (1,2). Since the analgesic potency in these cases was determined in the post-operative period so that an interaction with other drugs cannot be excluded, we determined nalbuphine's various actions in the absence of other agents in awake dogs.

Methods:

Increasing amounts of nalbuphine (20,40,80, and 160 mg) were injected at 5 min intervals to a total of 300 mg and its effects studied on pain responses (heart and blood pressure changes and somatic responses to tail clamping), respiration (respiratory rate, PaO_2, $PaCO_2$, pH), circulation (heart rate, arterial blood pressure) and oxygen consumption ($\dot{V}O_2$). After the last nalbuphine injection, the effect of fentanyl (80 μg/kg) was studied.

Results:

The results are shown in the figure. Except for a slight decrease in the respiratory (A) and an increase in heart rate (C), the recorded variables remained essentially constant during the injection period. In particular, nalbuphine did not alter the cardiovascular and behavioural response to noxious stimulation (D) induced by tail clamping. However, nalbuphine completely abolished the analgesic and cardiorespiratory actions of fentanyl (80 μg/kg). There were no recognizable changes in the animal's state of awareness throughout the course of experiment.



Discussion:

Nalbuphine did not affect the animals' somatic and behavioural response to noxious stimuli, nor did it produce cardiorespiratory opiate-like effects, even though it prevented fentanyl's analgesic and cardiorespiratory actions. Since the dose of fentanyl used has been shown to elicit maximal analgesia and respiratory depressant action in the same animals in a previous study (3), we concluded that nalbuphine has no agonist but a marked antagonist action at the opiate receptor in awake dogs.

References:

1. Ma uder MR, Delaney RD, DiFazio DA. Reversal of Na cotic-Induced Respiratory Depression With Na ouphine Hydrochloride. Anesthesiology Review 19 ;9:34-37.
2. La asch L, Probst S, Dudziak R. Reversal by Na ouphine of Respiratory Depression Caused by Fe tanyl. Anesth Analg 1984;63:814-816.
3. Ar dt JO, Mikat M, Parasher C. Fentanyl's An lgesic, Respiratory, and Cardiovascular Actions in Relation to Dose and Plasma Concentration in Un nesthetized Dogs. Anesthesiology 1984; 61 355-361.

Title: NAUSEA AND VOMITING AFTER OUPATIENT LAPAROSCOPY: INCIDENCE, IMPACT ON RECOVERY ROOM STAY AND COST.

Authors: SE Metter, M.D., DS Kitz, Ph.D., ML Young, M.D., AM Baldeck, M.D., JL Apfelbaum, M.D., JH Lecky, M.D.
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INTRODUCTION: Postoperative morbidity and duration of recovery room (RR) stay are important factors to consider in evaluating ambulatory surgery practice. Patient satisfaction, day surgery unit (DSU) utilization and per patient institutional costs are all compromised by extended RR stays. The purposes of this study were: 1) to test our clinical impression that a large proportion of patients who undergo diagnostic laparoscopy experience nausea (N) and vomiting (V) in the RR; 2) to determine whether these symptoms extend RR stay; and 3)to determine the impact of two common anesthetic agents -- fentanyl citrate (F) and isoflurane (I) -- on the incidence of N and V.

METHODS: We reviewed the charts of all 314 female patients who underwent diagnostic laparoscopy in our DSU between 7/1/84 and 6/30/85. Patient age, ASA physical status, surgeon, operative time, occurrence of N and V and duration of RR stay were recorded. (F) patients were anesthetized with $O_2/N_2O/F$ (0.2-0.3mcg/kg) and received a relaxant; succinylcholine for intubation and vecuronium or atracurium for maintenance. (I) patients were anesthetized with $O_2/N_2O/I$ and received succinylcholine to facilitate intubation. All patients received thiopental for induction. Chi-square tests and analysis of variance were used to determine the significance of differences among groups.

RESULTS: Nausea and Vomiting - Overall, there were no significant differences among the three RR groups (asymptomatic, nausea only, nausea and vomiting) with regard to age, physical status level or surgeon. Eleven percent of all patients experienced N only and an additional 18% of all patients experienced both N and V. There were significant differences among the groups in operative ($p<.02$) and RR times ($p<.001$, Table 1); RR stay was extended by 19 minutes for N patients and by 47 minutes for N and V patients when compared to asymptomatic patients. These differences resulted in increased RR labor costs, which are based on nurse and aide salaries and benefits.

Anesthetic Agents - There were no significant differences between the (F) and (I) subgroups with regard to age, physical status, surgeon or operative time. Asymptomatic patients in both subgroups stayed in the RR for 106 minutes, N patients for 118 minutes and N and V patients for 158 minutes ($p<.001$, Table 2). However, a significantly ($p<.03$) greater proportion of (F) patients (43%) experienced N or N and V than did (I) patients (25%, Table 3).

CONCLUSIONS: The incidence of RR N and V is high for patients undergoing diagnostic laparoscopy. N and V prolong RR stay and increase per patient labor costs. There is a higher incidence of N and V among patients receiving (F) than among patients receiving (I). This type of retrospective analysis provides a basis for evaluating institutional practice. Moreover, the results allow the selection of outcome variables and sample sizes necessary for prospective studies examining the impact of different anesthetic agents and surgical procedures on postoperative morbidity, duration of RR stay and cost.

Table 1: Mean Operative and RR Times (minutes) and RR Labor Cost by RR Group.

	Operative Time*	RR Time**	RR Labor Cost**
Asymptomatic (71%)	47	107	$12.84
Nausea Only (11%)	46	126	$15.12
Nausea, Vomited (18%)	53	154	$18.48

*$p<.02$ **$p<.001$

Table 2: Mean RR Time (minutes) and Labor Cost by RR Group.

	FENTANYL*	ISOFLURANE*	COMBINED*	RR LABOR COST*
Asymptomatic	97 min	108 min	106 min	$12.72
Nausea only	114 min	120 min	118 min	$14.16
Nausea, vomited	163 min	154 min	158 min	$18.96

*$p<.001$

Table 3: Percent of Patients by RR Group.

	FENTANYL N=54	ISOFLURANE N=163
Asymptomatic	57%	75%
Nausea only	13%	10%
Nausea, vomited	30%	15%
Total Nausea and Vomiting	43%	25%

$p<.03$

Title : ANALGESIC EFFECTIVENESS OF INTRATHECAL INHIBITORS OF ENKEPHALINASE AND AMINOPEPTIDASE IN MAN

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Introduction. Enkephalins are hydrolysed by various enzyme systems. Two of them seem to have a physiological function : an enkephalindipeptidylcarboxypeptidase ("enkephalinase", EC 3.4. 24.11) and an aminopeptidase activity (aminopeptidase M, EC 3.4.11.2). Thiorphan and bestatin inhibit these two enzyme activities, they protect endogenous enkephalins from extensive degradation and elicit naloxone-reversible antinociceptive effect in rodents (1,2,3). This study was designed to obtain information on the analgesic effectiveness of intrathecal Thiorphan and bestatin in man.

Methods. With institutional approval and informed consent, five patients with terminal cancer (maintained pain-free with 1.5 mg/24h of intrathecal morphine prior to the present study) received randomly and in a double-blind manner several intrathecal injections of either peptidase inhibitors or saline. When patients complained of severe pain, injections were performed under a volume of 3 ml via a subarachnoid catheter and a subcutaneous reservoir (Spinalgesic drug delivery system®, AHS-France). They consisted of 0.0125 mg Thiorphan (T, n=12), 1.55 mg bestatin (B, n=14), 0.0125 mg Thiorphan plus 1.55 mg bestatin (T + B, n=18) or saline (S, n=5). For ethical reasons, S was administered only once per patient as a control. Pain scores were assessed on a visual analogue scale (no pain = 0, worst pain = 10). The time until onset of analgesia (TOA), the percent decrease in pain score (%DPS) and the duration of the analgesic effect (DA) were evaluated. For technical reasons in only one case could radioimmunoassay of CSF met-enkephalin concentration be performed prior to (met-enk-0) and 2 hours after (met-enk-2h) intrathecal injection of T + B.

Results. Analgesia was obtained following 7 (out of 12) injections of T, 11 (out of 14) injections of B, 15 (out of 18) injections of T + B but only after one (out of 5) injections of S. Analgesia generally occurred within 20 min. after injections. Following intrathecal T + B, %DPS was significantly higher and DA was significantly longer than after T, B or S alone (see Table 1). CSF met-enk-0 was 0.233 pmol/ml and met-enk-2h was 0.440 pmol/ml. No side effects were observed.

Discussion. These results are in accordance with recent data demonstrating that administration of T + B into the CSF of mice produces a more effective analgesia than that produced by T or B injected alone (3). Moreover they tend to confirm that T + B protect endogenous opioids in humans like in rodents (3). Finally these data suggest that inhibition of endogenous opioid inactivating peptidases might constitute a novel therapeutic approach in the treatement of intractable cancer pain.

References.

1. Roques BP, Fournié-Zaluski MC, Soroca E, Lecomte JM, Malfroy B, Llorens C, Schwartz JC. The enkephalinase inhibitor thiorphan shows antinociceptive activity in mice. Nature 1980; 288:28[illegible]-288.
2. Chaillet P, Marçais-Collado H, Costentin J, Yi CC, De La Baume S, Schwartz JC. Inhibition of enkephalin metabolism by, and antinociceptive activity of, bestatin, and aminopeptidase inhibitor. Eur J Pharmacol 1983; 86:329-336.
3. De La Baume S, Yi CC, Schwartz JC, Chaillet P, Marçais-Collado H, Costentin J. Parcicipation of both "enkephalinase" and aminopeptidase activities in the metabolism of endogenous enkephalins. Neuroscience 1983; 8:143-151.

	Saline	Thiorphan (0.0125mg)	Bestatin (1.55mg)	Thiorphan + Bestatin
No injections	5	12	14	18
%DPS (±SD)	8 ***	38±11 **	55±5 *	80±8
DA (h±SD)	3 ***	3.7±1.1 **	6.5±2.3 **	18.1±4.7

Table 1

Title: OUTPATIENT ANESTHESIA: RECOVERY AFTER PROPOFOL, METHOHEXITAL AND THIOPENTAL

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Introduction. Outpatient surgery is becoming increasingly popular for both social and economic reasons. The anesthesiologist is required to provide a smooth induction combined with good operating conditions and a rapid recovery with minimal sequelae. Thiopental has a prolonged action and despite the high incidence of excitatory effects methohexital is frequently preferred for outpatient work.

Propofol, a new non-barbiturate intravenous anesthetic agent has a short elimination half-life of about 1 hr which should ensure a rapid post-operative recovery (1).

We here compare the recovery characteristics of equivalent doses of propofol(P), methohexital(M) and thiopental(T) for induction of outpatient anesthesia.

Method. Healthy unpremedicated patients aged 16-55 yr, weighing 45-80 kg scheduled for minor gynecologic outpatient operations were randomly allocated to one of three groups of 25. Anesthesia was induced with either P 2.5 mg/kg, M 1.5 mg/kg or T 5 mg/kg and maintained with 66% nitrous oxide in oxygen with isoflurane (IF) via a face mask. The inspired concentration of IF was rapidly increased to 3% reducing to 1% once anesthesia was established. The quality of induction was assessed subjectively. Ethical approval was obtained.

A second observer, unaware of the induction agent used, assessed recovery using clinical (subjective) and psychomotor (objective) criteria. Initial clinical observations included time to eye opening, orientation in time and place and giving correct date of birth (DOB). Subsequently an assessment of alertness using a 4 point scale, and ataxia (steadiness) at 20, 40 and 60 min postoperatively was carried out.

Psychomotor testing (2) consisted of four choice reaction times (CRT) performed at 20, 40 and 60 min postoperatively and compared with preoperative values. Identical testing was undertaken by a control group (C) of 25 non-anesthetized patients. The patients scanned four lamps which lit in random order and immediately pressed the appropriate button to extinguish the light. The responses were subsequently decoded and analysed by computer. The latency of this response is an accurate measure of psychomotor performance (3).

Postoperative sequelae such as headache, nausea and vomiting were also noted.

All findings are expressed as mean ± sem.

Results. The groups were broadly comparable with respect to age, weight and duration of anesthesia. Induction was smoothest with P with only 1 induction being assessed as poor compared to 7 with M and 2 with T. Cardiovascular depression was more marked with P, the mean fall in systolic pressure averaging 13% compared with 2% for M and 6% for T. Apnea of more than 60 sec occurred in 2 P, 3 T and no M inductions.

Table 1 shows that with all subjective tests recovery was significantly slower with M and T than with P ($p < 0.01$).

Table 1. Clinical Recovery Times

Minutes to	P	M	T
Eye opening	6.8 ± 0.5	10.7 ± 0.7	9.7 ± 0.7
Correct DOB	7.2 ± 0.5	11.1 ± 0.7	10.1 ± 0.7
Orientation	7.2 ± 0.5	11.2 ± 0.7	10.4 ± 0.6

Ataxia was common in all groups 20 min postoperatively but after 40 min only 2 patients who had received P were still affected compared with 9 M and 17 T. Similarly alertness scores were reduced in the M and T groups compared to the P group at 20 and 40 min postoperatively. With both these tests recovery after P was significantly better than after M or T.

Table 2. Changes (m sec) from baseline CRT values.

Min	C	P	M	T
20	-47 ± 9	+29 ± 16	+71 ± 23	+178 ± 43**
40	-85 ± 8	-40 ± 16	-33 ± 18	+15 ± 33
60	-104 ± 9	-69 ± 16	-67 ± 14	-43 ± 27

+ indicates deterioration - indicates improvement
** $p < 0.01$ compared to P

At 20 min the changes in CRT (Table 2) were less with P than with the other two induction agents, but T only produced a significantly prolonged CRT as compared with the new drug. Although recovery with M was shorter than with T ($p < 0.01$) the difference was not as marked as between P and T. At 40 and 60 min there were no statistical differences between the groups. At all times of observation CRT performance was better in control than in anesthetized patients ($p < 0.05$).

Minor postop. sequelae were more common after T (5 nausea, 9 headache) than after M (3 nausea, 6 headache) or P (3 nausea, 3 headache).

Conclusion. Despite some cardiorespiratory depression propofol induction was smoother and both the speed and quality of recovery were superior to that of methohexital and thiopental. Propofol appears to offer significant advantages for outpatient anesthesia.

References

1. Briggs LP, White M, Cockshott ID, Douglas EJ. The pharmacokinetics of propofol ('Diprivan') in female patients. Postgrad Med J 1985; 61(Suppl 3): 58.
2. Wilkinson RT, Houghton D. Portable four choice reaction time test with magnetic tape memory. Behaviour Res Meth Instrument 1975; 7: 441.
3. Hindmarch I. Psychomotor function and psychoactive drugs. Br J Clin Pharmac 1980; 10: 189.

Title: EVALUATION OF VECURONIUM NEUROMUSCULAR BLOCKADE IN PEDIATRIC PATIENTS WITH THERMAL INJURY

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Introduction. Patients with burns require increased doses of non-depolarizing muscle relaxants (NDMR) to achieve a given effect (1). We studied the pharmacology of vecuronium, an intermediate-duration NDMR to determine: (a) if patients with burns exhibit similar resistance,

(b) if degree of resistance is related to burn size,

(c) dose-response curves for minor, moderate, and major burns.

Methods. Institutional approval was obtained through the Human Studies Committee and permission was obtained from patient and/or guardian. Twenty patients, ranging in age from 3 to 17 years, were studied a total of 30 times. No patient had any serious medical problem or neuromuscular disease prior to their burn, and none had any major organ failure at the time of study. Pre-operative medication was limited to diazepam (0.05-0.20 mg/kg po) and/or morphine (0.10-0.15 mg/kg im or iv) with the exception of very young patients, some of whom received methohexital (25-30 mg/kg pr).

Anesthesia was induced with thiopental (4-6 mg/kg iv) and N_2O/O_2 (60:40) by mask. In some infants, halothane was given by mask until an intravenous cannula was established; in these patients, studies were not commenced for a minimum of 10 minutes after discontinuation of the halothane. Narcotics (morphine or fentanyl iv) were administered as anesthetic supplements. Neuromuscular blockade was judged by thumb adduction force as measured by a GRASS force transducer using evoked single twitch responses (0.15 HZ) of the ulnar nerve/adductor pollicus system. Following establishment of stable anesthesia, hemodynamics and twitch tension, vecuronium was administered. Because of vecuronium's relatively short duration of action, it was given by the bolus dose technique described by Fisher et al (2). Patients were grouped as follows: Group 1 (controls) were those not suffering from an acute burn. Groups 2-4 were those with acute burns who were studied at least 7 days after burn. Group 2 (minor) - less than 40% total body surface area (TBSA), Group 3 (moderate) - 40-60% TBSA, Group 4 (major) - greater than 60% TBSA. Results were examined by analysis of co-variance.

Results. In controls our ED values were similar to the ED values of others despite different anesthetic technique or mode of administration (3,4). For example, the ED_{50} in normal children, by single bolus technique, was 19 µg/kg compared to 18 µg/kg in our controls (4). The ED values of the acutely burned patients were significantly different ($p < 0.001$) from controls (Table 1). The slopes of the dose-response curves on the different groups of acutely burned patients were not found to be significantly different ($p= 0.43$).

TABLE 1 ED Values of Vecuronium (µg/kg)

	ED_{50}	ED_{95}
Controls	18	35
<40% Burn	34	68*
40-60% Burn	55	111*
>60% Burn	65	129*

*$p < 0.001$ compared to controls

Discussion. This study documents that acutely burned patients are hyposensitive to the neuromuscular effects of vecuronium. This is consistent with the observation with other neuromuscular relaxants (1). The hyposensitivity is related to the magnitude of burn injury (Table 1). That is, patients with bigger burns require a larger dose of vecuronium to achieve the same effect. The ED_{95} of acutely burned patients with >60% burn is 129 µg/kg which is approximately 3.5 times higher than ED_{95} in controls. In order to achieve rapid onset paralysis as a replacement for succinylcholine which is contraindicated in burns very much higher doses may have to be administered (4).

Conclusions. Since thermally injured patients show relative hyposensitivity to vecuronium, and degree of resistance is directly correlated to extent of burn, vecuronium doses have to be adjusted upwards accordingly to achieve effective neuromuscular paralysis. The cardiovascular and neuromuscular effects of vecuronium as an alternative to succinylcholine deserves further study.

References

1. Martyn, JAJ, Clinical pharmacology and drug therapy in the burned patient, Anesthesiology 65:67-75, 1986.
2. Fisher, DM, Miller, RD, Potency determination for vecuronium. Comparison of cumulative and single-dose techniques. Anesthesiology 57:309-310, 1982.
3. Goudsouzian, NG, Martyn, JAJ, Liu, LMP et al, Safety and efficacy of vecuronium in adolescents and children. Anesth. Analg. 62:1083-1088, 1983.
4. Miller, RD, Rupp, SM, Fisher, DM et al, Clinical pharmacology of vecuronium and atracurium, Anesthesiology 61:444-453, 1984.

Title: Reducing Blood Loss from Nasotracheal Intubation by Combining a Warmed Tube with Vasoconstrictors

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Introduction. Sequential nasal dilation[1] and warming the endotracheal tube[2] have been reported to decrease the bleeding associated with nasal intubation. Theoretically topical vasoconstrictors may also decrease the bleeding. We tested the hypothesis that a warm endotracheal tube (WT), plus using vasoconstrictors (VC) would further decrease the bleeding associated with nasal intubation (NT).

Methods. We studied 60 consecutive patients, ASA I or II, scheduled for elective maxillofacial surgery who required nasal intubation. We excluded patients with known bleeding disorders or obvious abnormal nasal anatomy. Each of the intubation methods used in this study is commonly used at our institution. All staff agreed to randomized and double-blind 60 consecutive cases among the six groups below: (1) Control: no vasoconstrictor and room temperature tube (RT); (2) 0.05% oxymetazoline hydrodioxide (AFRIN) and RT; (3) 4% cocaine and RT; (4) no vasoconstrictor and warmed tube (WT); (5) AFRIN and WT; (6) 4% cocaine and WT. The anesthetist was given an unlabeled solution in an atomizer that contained either AFRIN, cocaine or sterile water with 1% methylene blue just prior to the procedure. Topicalization of the nasal airway was accomplished by atomizer. Time between topicalization and intubation averaged 15 minutes (range 10 to 30). Warmed tubes (WT) were placed in a blanket warmer for 5 minutes at a temperature of 165 degrees F prior to use. Patients were induced with 5-7 mg/kg of intravenous sodium thiopental. The nasal tube (RT or WT) was lubricated with 2% xylocaine jelly and placed through the nose, into the hypopharynx. Succinylcholine 1.5 mg/kg was then given intravenously to facilitate laryngoscopy and the tube was placed in the trachea under direct vision. After intubation and suctioning the pharynx, blood loss was graded by the following scale:[2] (1) None - no blood seen (2) Slight - blood in suction tip or first 6 inches of tubing (3) Moderate - blood in more than 6 inches of suction tubing (4) Severe - blood reaching suction cannister or inhibiting intubation attempt. The independent grades from the oral surgeon and the anesthesia staff were averaged. Statistical analysis was by unpaired Students t-test.

Results. The overall incidence of any bleeding (score >1) was 78% in RT (groups 1 to 3) compared to 35% for WT (groups 4 to 6) ($p < .05$). Compared to control (group 1) cocaine-RT, AFRIN-WT, and cocaine-WT reduced bleeding ($p < .05, < .01$, and $< .01$ respectively). See Table 1.
Figure 1 shows the effect of the topical vasoconstrictors AFRIN and cocaine on the blood loss when using a RT or WT. Addition of warmed tubes to regimen only decreased blood loss significantly when AFRIN was also used ($p < .05$). The decrease with cocaine did not reach statistical significance.

Discussion. This study confirms that simply warming endotracheal tubes reduces bleeding associated with nasal intubation. The decreased incidence and severity of bleeding may be due to the ability of softened tube to conform to nasal structures which aided passage through the nose. The use of the vasoconstrictors AFRIN or cocaine with warmed tubes further reduced blood loss. Cost considerations, availability, its unscheduled drug status, and equal efficacy to cocaine make AFRIN a reasonable alternative when used with a warm endotracheal tube.

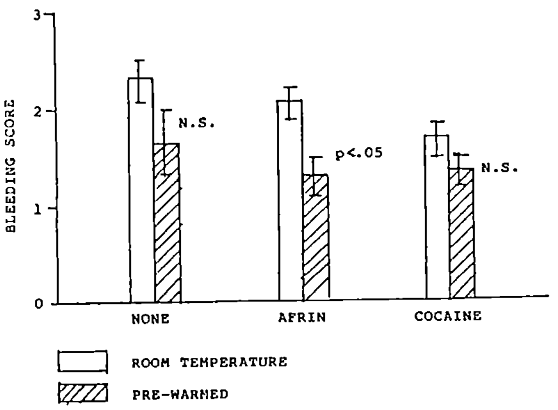
References.

1. Kay J, et al: Sequential dilation. A useful adjunct in reducing blood loss from nasotracheal intubation. Anes 1985; 63(3A):A259.
2. Quintin L, et al: Decreasing the incidence of upper airway bleeding when using a large size nasotracheal tube. Anesthesiology 1985; 62:374.

Table 1. Bleeding Scores Following Nasotracheal Intubation

Group	MEAN	SEM	P
1 (none- RT)	2.29	± .217	
2 (AFRIN- RT)	2.08	± .177	NS
3 (Cocaine- RT)	1.63	± .164	<.05
4 (none- WT)	1.68	± .288	NS
5 (AFRIN- WT)	1.27	± .195	<.01
6 (Cocaine- WT)	1.30	± .152	<.01

FIGURE 1: BLOOD LOSS SCORE WITH VARIOUS VASOCONSTRICTORS



Title: EVALUATION OF THE ANALGESIC EFFECT OF EPIDURAL KETAMINE

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Introduction. Subanesthetic dose of ketamine has been shown to possess an analgesic effect in animal and human studies (1). Recently several studies indicated that the analgesic produced by ketamine is mediated by opiate receptors (2). Furthermore, ketamine's lack of respiratory depressing effects offers an advantage over the narcotic analgesics. The present study was undertaken to evaluate the analgesic effect of ketamine when administered epidurally in patients with postoperative pain.

Method. The study was conducted after institutional approval and informed consents were obtained from all the patients prior to their entry into the study. Forty adult patients scheduled for upper abdominal surgeries were enrolled in this study. All patients received thiopental induction and inhalation anesthesia with halothane or enflurane in nitrous oxide and oxygen with no narcotic agents added. At the completion of surgery, before awakening from anesthesia, an indwelling epidural catheter was placed in patient's lower thoracic area (T_{10}-T_{12}). After patients fully recovered from anesthesia and complained of pain in the postoperative period, ketamine hydrochloride, 15 mg in 10 ml normal saline, was administered epidurally via the catheter and all the patients were observed for pain intensity scores (by visual analogue scale), pain relief scores (0 = none, 1 = 25%, 2 - 50%, 3 = 75%, and 4 = complete), vital signs and side effects for 24 hours. "Rescue" medication, meperidine 50-75 mg intramuscularly, was given whenever a patient complained of inadequate pain relief.

Results. Onset of pain relief with epidural ketamine appeared at 5 minutes, peaked between 20-30 minutes with a duration of action averaging 3.8 ± 1.6 hours S.D. (Table I). No evidence of sensory, motor or autonomic blockade were observed in any patient nor was there any incidence of pruritis, urinary retention or respiratory depression. Four patients complained of dizziness and feeling of detachment. There was no significant change in both systolic and diastolic blood pressure and heart rate after drug administration.

Discussion. Islas and associates reported that epidural ketamine 4 mg provided postoperative analgesia with a mean duration of 4.06 ± 1.34 hours (3). Our study demonstrated that while utilizing a much larger dose, epidural ketamine at 15 mg provided effective analgesia in postsurgical patients, but its duration of action is still much shorter than that reported in most studies of epidural morphine. Furthermore, in 4 (10%) patients early signs of psychotomimetic effects were observed and this raises the question whether it will be advisable to administer ketamine epidurally at an even larger dose to strive for more prolonged pain relief. In conclusion, epidural ketamine appears to provide efficacious pain relief but its relatively short duration of action and psychotomimetic effects might restrict its usefulness as a replacement for epidural opiates.

References.

1. Slogoff S, Allen GW, et al: Clinical experience with subanesthetic ketamine. Anesth Analg 53:354-358, 1974.
2. Finck AD, Ngai SH: Opiate receptor mediation of ketamine analgesia. Anesthesiology 56:291-297, 1982.
3. Islas JA, Astroga J, Loredo M: Epidural ketamine for control of postoperative pain. Anesth Analg 64:11[illegible]-1162, 1985.

PAIN SCORES AFTER INJECTION OF EPIDURAL KETAMINE

TIME	0	5	10	20	30 min.
VISUAL ANALOGUE	7.6 ± 0.18	3.9 ± 0.31*	2.8 ± 0.19*	2.5 ± 0.16*	2.5 ± 0.18*
PAIN RELIEF	0	2.5 ± 0.8	2.7 ± 0.8	2.8 ± 0.7	2.8 ± 0.9

TIME	1	2	3	4	5 hrs.
VISUAL ANALOGUE	3.1 ± 0.28*	4.2 ± 0.35*	5.4 ± 0.34*	6.2 ± 0.31	7.1 ± 0.35
PAIN RELIEF	2.4 ± 0.8	2.1 ± 0.9	1.6 ± 0.2	1.0 ± 0.2	0.8 ± 0.6

*$p < 0.05$

Title:

THE EFFECT OF H_2 RECEPTOR BLOCKERS ON BUPIVACAINE DISPOSITION

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Introduction H_2 receptor antagonists cimetidine (1) and ranitidine (2) have differing effects on the disposition of lignocaine. Both blockers are used in obstetric practice to decrease gastric acidity and their use is commonly associated with the use of bupivacaine for extradural anesthesia. There is justifiable anxiety concerning the interaction of local anesthetics and H_2 receptor blockers (3), since a study comparing the effects of adrenaline on the uptake of extradurally administered bupivacaine for elective Cesarean section showed a significant elevation of plasma bupivacaine levels in women receiving ranitidine as their antacid therapy (Fig. 1) (4).

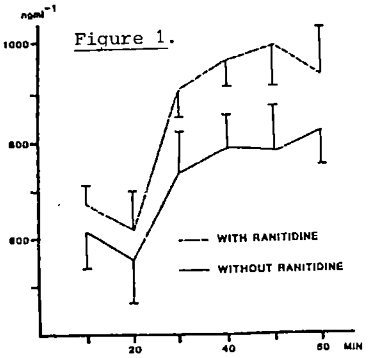

Figure 1.

MEAN PLASMA BUPIVACAINE LEVELS (±SEM)

A more definitive investigation of the effects of pretreatment with cinetidine and ranitidine in the uptake, distribution and elimination of bupivacaine given extradurally to patients undergoing elective Cesarean delivery seemed indicated and the findings are reported here.

Methods Only healthy women, at term, awho selected extradural anesthesia for elective Cesarean section were included. They had no relevant past history and were not on any medication. Patient and local Ethical Committee approval was obtained.

They were randomly allocated to 3 groups. These were given either cimetidine 400 mg, ranitidine 150 mg or no pretreatment. The H_2 blockers were given orally 90 min prior to instituting the extradural block. Bupivacaine 0.5% was the local anesthetic used. The initial dose was 10 ml and incremental doses at 20 min intervals were given, calculated as 1.5 ml per unblocked segment below T_6.

Venous blood was collected from an antecubital vein of the non-infused arm via a 16 guage catheter. Samples were collected before and at 10 min intervals from the first dose of bupivacaine for 90 min then at 2, 3, 4 and 5 hr. The samples were centrifuged and the supernutant plasma stored at -20°C until analysis. Bupivacaine estimations were made using HPLC with UV detection at 220 nm. Mepivacaine was used as the standard.

Results Eighteen patients were included in the study and were equally distributed between the 3 groups. The plasma bupivacaine levels show that (Table 1) following both cimetidine and ranitidine pretreatment levels were higher than in the control group. None of the between-group differences were statistically significant due to marked variation of bupivacaine levels in those given H_2 blockers.

Table 1. Mean plasma levels of bupivacaine (ng/ml ± SE) following its extradural administration to patients given no treatment, cimetidine 400 mg or ranitidine 150 mg orally.

Min	Control	Ranitidine	Cimetidine
10	415 ± 31	699 ± 171	607 ± 106
20	431 ± 26	611 ± 130	570 ± 95
30	592 ± 50	711 ± 161	911 ± 165
40	689 ± 30	777 ± 149	956 ± 184
50	701 ± 74	740 ± 101	875 ± 159
60	637 ± 68	752 ± 115	855 ± 135
70	613 ± 55	723 ± 142	808 ± 80
80	518 ± 50	714 ± 186	744 ± 60
90	470 ± 42	619 ± 87	670 ± 69
2 hr	391 ± 37	580 ± 80	559 ± 98
3 "	267 ± 16	432 ± 69	410 ± 75
4 "	218 ± 17	301 ± 37	324 ± 53
5 "	173 ± 14	231 ± 32	311 ± 55

Discussion Cimetidine but not ranitidine has been shown to inhibit the metabolism of a wide variety of drugs and this difference has been attributed to the presence of an imidazole ring in the cimetidine molecule (5). This study suggests that both H_2 receptor blockers effect the pharmacokinetic profile of extradurally administered bupivacaine and that further investigation is required.

The similarity in the time course of decay in plasma bupivacaine levels in those women who did and did not receive H_2 blocker treatment suggests that the higher concentration in the former series indicates a change in volume of distribution rather than an effect on metabolism.

Accepting a variation of 6% in the method of bupivacaine estimation and a 40% within-group variation numbers required to give a 95% chance of showing a clinically significant difference (50%) between control and those pretreated with H_2 receptor blockers is 18 per group.

References

1. Feely J, Wilkinson GR, McAllister CB, Wood AJJ. Increased toxicity and reduced clearance of lidocaine by cimetidine. Ann Int Med 1982; 96: 592.
2. Feely J, Guy E. Lack of effect of ranitidine on the disposition of lignocaine. Br. J. Clin. Pharmac., 1983; 15: 378.
3. Hodgkinson R. Potential interactions between cimetidine and amide local anesthetics in obstetrics. Anesthesiology 1984; 60: 508.
4. Wilson CM, Moore J, Ghaly RG, Flynn RJ, McClean E, Dundee JW. Plasma concentrations of bupivacaine during extradural anaesthesia for Caesarean Section: the effect of adrenaline. Anaesthesia 1987; 42:
5. Henry DA, MacDonald IA, Kitchingman G, Bell GD, Langman MJS. Cimetidine and ranitidine: comparison of effects on hepatic drug metabolism. Br Med J 1980; 281: 775.

TITLE: A COMPARATIVE STUDY OF DIPRIVAN AND THIOPENTAL AS INDUCTION AGENTS IN DENTAL PATIENTS

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INTRODUCTION Diisopropylphenol (Diprivan) is a new intravenous induction agent which is insoluble in water and thus is supplied as a 1% emulsion. The purpose of this study was to evaluate and compare the efficacy, cardiovascular and respiratory changes, recovery characteristics and side effects of diprivan (2.5mg/Kg) with thiopental (5.0mg/Kg) for the induction of general anaesthesia in fit dental outpatients.

METHODS Institutional approval of the study was obtained. After signing informed consent 43(ASA Class I or II) patients were enrolled into the study. All patients were scheduled for minor dental surgical procedures performed as an outpatient. All patients received a premedication of meperidine 1mg/Kg intramuscularly one hour prior to the booked surgery. Patients were randomised on a 2=1 basis to 2 groups - Group I received Diprivan 2.5mg/Kg and Group II Thiopental 5mg/Kg administered intravenously over 20 seconds as an induction agent. If the patient did not fall asleep within 1 minute 25% of the induction dose was administered as an increment. Gallamine 15mg and succinylcholine 1.5mg/Kg were administered intravenously to facilitate nasotracheal intubation after a 3 minute period during which the patient breathed 100% O_2 by mask. During this period ECG was monitored, blood pressure measured at one minute intervals, and minute volume recorded using a Wrights' electronic respirometer. In addition the presence of pain on injection or other side effects were noted. All observations were made by a trained observer who was unaware of the agent being used, as also was the patient. During the 3 minute period following induction an increment equal to 25% of the induction dose was given if deemed necessary to maintain anaesthesia. Anaesthesia was then maintained with nitrous oxide 70% in oxygen, and isoflurane 1-2% with spontaneous respiration. At the end of surgery anaesthesia was stopped and recovery times (open eyes, obey a simple command and recall birthdate) were recorded. In addition the observer noted side effects and venous sequelae were followed up for 14 days postoperatively (the induction agent was injected into an intravenous line not used for any other medication). Statistical analysis was by analysis of variance and unpaired T test for continuous data and Fischer exact test for binary data, and $p \leq 0.05$ was regarded as being statistically significant.

RESULTS 28 patients (25.0±1.9 years, 24 male) received diprivan and 15 patients (25.5±1.9 years, 10 male) received thiopental. The heights and weights of the patients in the two groups were similar. 3(11%) of the diprivan patients required a 2nd dose for induction, compared to none of the thiopental. However 2(13%) of the thiopental required a 2nd dose in the 3 minute period following induction compared to none of the diprivan. 20(71%) of the diprivan group developed apnoea compared to 10(67%) of the thiopental group and in 9(32%) diprivan patients and 4(27%) thiopental patients the apnoea lasted more than 60 seconds requiring assisted ventilation. 4 diprivan patients complained of pain or discomfort on injection, whereas none of the thiopental group did so and no venous sequelae were noted in any patient.

The haemodynamic data are shown in Figure I. The blood pressure was significantly lower in the diprivan group as follows - systolic pressure at 3 minutes (p=0.02) and diastolic pressure at both 2 minutes (p=0.001) and 3 minutes (p=0.05). The respiratory data and times for recovery are shown in Table I. In the diprivan group the minute volume was significantly less at 2 minutes after induction than in the thiopental group. The times for recovery were significantly shorter in the diprivan group for each category measured. Side effects occurred in similar frequency in each group except for nausea and vomiting which was present in 5(18%) of the diprivan patients compared to 8(53%) of the thiopental.

CONCLUSIONS Diprivan would appear to be an effective induction agent for fit outpatients undergoing dental surgery. Its use was associated with a higher incidence of mild cardiovascular and respiratory depression when compared to thiopental. However the diprivan patients recovered significantly faster and had less nausea and vomiting and thus it would appear to be a promising induction agent for use in outpatients.

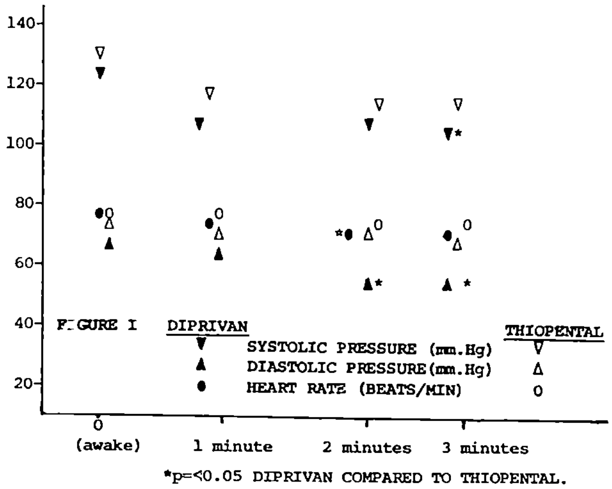

FIGURE I

TABLE I

DATA		Mins	DIPRIVAN	THIOPENTAL	P
Minute Volume (Liters)		0	7.7±0.4	8.7±0.6	
		1	5.3±0.4	5.3±0.5	
		2	4.2±0.4	5.7±0.4	0.01
		3	7.0±1.0	6.5±0.5	
RECOVERY	OPEN EYES (min)		6.9±0.8	10.5±1.6	0.05
	OBEY COMMAND (min)		7.6±0.8	11.1±1.6	0.05
	BIRTHDATE (min)		8.2±0.8	12.4±1.7	0.02

RESPIRATORY DATA & RECOVERY TIMES
(mean±S E M)

Title: INCIDENCE OF BRACHIAL PLEXUS STIMULATION DURING INTERNAL JUGULAR VEIN CANNULATION

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Introduction. Several mechanisms of perioperative brachial plexus (BP) injuries in open heart surgery have been proposed and include hyperabduction of the arm at the shoulder, excessive sternal retraction, and iatrogenic first rib fractures. But despite alterations of surgical technique and intra-operative patient positioning, BP injuries still occur. Recently Hansen et al. demonstrated that 73% of post-operative BP injuries occurred at the ipsilateral side of internal jugular vein (IJV) cannulation in open heart surgery.[1] They postulated that traumatic cannulation may be a major mechanism of plexus injury. This investigation used a nerve stimulator attached to the metal cannulas used during IJV cannulation to determine the incidence of stimulation of the BP.

Methods. With informed consent and approval of the Human Subjects Review Committee, we evaluated 20 patients scheduled for open heart surgery. The patients were premedicated with lorazepam 0.04 mg/kg and morphine 0.1 mg/kg. Each patient's height, weight, and neck circumference were recorded. Intravenous and arterial catheters were placed percutaneously under local anesthesia, and EKG leads were placed. A nerve stimulator ground lead was placed on the right (R) shoulder. The R neck was prepped and draped and the patient placed in a 30-degree Trendelenburg position. The two heads of the sternocleidomastoids were identified so that the central approach to the R IJV could be performed. Using an 8.5 Fr Arrow introducer tray, we infiltrated 1-2 cc's of 1% xylocaine subcutaneously prior to the insertion of a 22-gauge "seeker" (S) needle. A sterile lead was attached to the S needle and to a Bard model 750 nerve stimulator. The stimulus frequency was 1 impulse/sec, and the voltage was set between 4 and 5 volts which will cause nerve stimulation when the needle is 3 mm from the nerve.[2] The S needle was then advanced into the apex of the triangle toward the R nipple at a 45-60° angle with the frontal plane until the R IJV was identified. Any movement of the patient's fingers, forearm, or arm was noted and recorded by an independent observer, and the needle advancement was stopped and redirected. After the S needle identified the IJV, the lead was then placed on the 18 gauge x 2 1/2" thin walled (TW) needle used to cannulate the R IJV. This needle was inserted along the path of the S needle until blood was aspirated. The nerve stimulator was set at the previous parameters, and clinical movement was again noted and recorded. The lead was then removed and the guide wire was placed. The introducer was then placed into the R IJV over the guide wire. All cannulations were performed by third-year residents or anesthesia fellows. Neurologic examinations were performed pre- and post-operatively. Statistical analysis was performed by one-way analysis of variance and non-parametric Kruskal-Wallis tests.

Results. All patients had the R IJV successfully cannulated. Most patients required fewer than three passages of the S needle to identify the R IJV. The mean numbers of attempts with the S needle was lower in patients who weren't stimulated, but this difference was not statistically significant (Fig. 1). Two of twenty patients elicited motor stimulation of the BP during location of the R IJV with the S needle. No patients were stimulated when the TW needle was placed. There were no demographic differences between those patients who were stimulated and those who were not. No parasthesias were noted throughout the study. No postoperative neurologic dysfunction in either upper extremity was noted.

Discussion. Data from our investigation supports the concept of Hanson et al. that IJV cannulation can be a cause of post-operative BP neuropathy. The 10% incidence of stimulation may appear high, but it may reflect the experience of the physician performing the cannulation. Because we did not advance the needles once stimulation had occurred, we didn't have any patients with neurologic dysfunction. Since the needle tip was only 3-4 mm away from the nerve, it seems very plausible that further advancement into the BP could have occurred. Since most patients presenting for open heart surgery are heavily premedicated, they may not complain of a parasthesia and injury may occur.

References

1. Hanson HR, Bleur AC, Furlan AF, et al: Mechanism and frequency of BP injury in open heart surgery: A prospective analysis. Annals of Thoracic Surgery 36:675-679, 1983

2. Greenblatt GM and Denson JS: Needle nerve stimulator-locator: Nerve blocks with a new instrument for locating nerves. Anesth and Analg 41:599-602, 1962

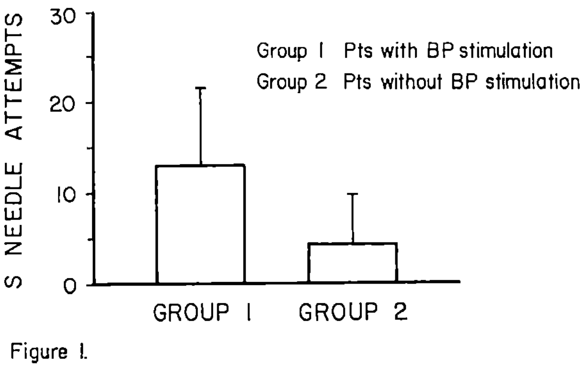

Figure 1.

TITLE:
THE INFLUENCE OF NON-PULSATILE NORMOTHERMIC PERFUSION ON CEREBRAL BLOOD FLOW AND METABOLISM

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Introduction: Cardiopulmonary bypass (CPB) may adversely influence cerebral blood flow (CBF) and metabolism. A 30% reduction in cerebral glucose consumption in pigs was seen during normothermic CPB.[1] Our study was designed to assess the influence of normothermic non-pulsatile CPB on cerebral oxygen consumption ($CMRO_2$) and CBF in man.

Methods: Following approval from the hospital human investigations committee and after obtaining written consent, 5 patients undergoing surgery for accessory ventricular pathway cryoablation were investigated. Anesthesia was induced and maintained by inhalation of isoflurane in oxygen. No other CNS depressants were used. Following sternotomy, anesthesia for each patient was maintained at a constant inspired isoflurane concentration throughout the study period, varying from 1.25% to 2.5% among patients. CBF was measured using 5mCi of ^{133}Xe in 6 ml saline injected into either the antecubital vein (pre- and post-CPB) or the arterial port of the pump oxygenator (during CPB). For intravenous studies, end-tidal ^{133}Xe was used to correct for recirculation. Mean CBF was based on the average ^{133}Xe clearance measured by 10 scintillation detectors located 5 over each cerebral hemisphere. Standard correction factors were used to compensate CBF values for changes in temperature and hematocrit. A 15 cm 16 ga catheter was introduced percutaneously and threaded retrograde into the right internal jugular bulb for sampling effluent cerebral venous blood. Blood gas measurements were made on a Radiometer ABL2 and oxygen saturation was measured directly using a Radiometer OSM3 hemoximeter. $CMRO_2$ was calculated as the product of the O_2 content difference between arterial and jugular venous blood and mean CBF. Measurements were made at three times: (1) following sternotomy, prior to CPB, (2) 15 to 30 min after commencement of CPB, (3) 15 to 30 min following termination of CPB. Data were analyzed using one-way ANOVA with Scheffe´s test for comparisons between events.

Results: Results are presented in the table (mean ± S.D.). For CBF and $CMRO_2$ each patient was his own control, data being expressed as percent of the pre-CPB value. During normothermic CPB, $CMRO_2$ was significantly reduced to 63% of the pre-CPB values. The 27% reduction in CBF did not achieve statistical significance. After weaning from CPB both $CMRO_2$ and CBF returned to their pre-CPB control values.

Discussion: Our study has demonstrated a 37% reduction in $CMRO_2$ during normothermic CPB in man. This is about half of the $CMRO_2$ depression seen with hypothermic (25°C) non-pulsatile CPB.[2] These data are consistent with studies in animals[1,3] and suggest that loss of pulsatile perfusion per se reduces $CMRO_2$. The mechanism remains speculative. Further studies examining the cerebrovascular effects of pulsatile and non-pulsatile CPB are required.

References:
1. Anderson A, Waaben J, Husum B, Voldby B, Bodker A, Hansen AJ, Gjedde A. Non-pulsatile cardiopulmonary bypass disrupts the flow-metabolism couple in the brain. J Thorac Cardiovasc Surg 1985;90:570-579.
2. Murkin JM, Farrar JK, Tweed WA, Guiraudon G, McKenzie FN. Relationship between cerebral blood flow and O2 consumption during high-dose narcotic anesthesia for cardiac surgery. Anesthesiology 1985;63:A44.
3. Horecky J, Sujansky E, Cerven J, Pappova E. Some problems of extracorporeal circulation with respect to the cerebral circulation. J Cardiovasc Surg 1966;7:79-83.

Table. Data for Five Subjects

	Pre-CPB (1)	CPB (2)	Post-CPB (3)
$CMRO_2$ (% control)	100	63±15*	103±21
CBF (% control)	100	73±32	107±42
MAP (mmHg)	74±5	54±5*	63±5
Temperature (°C)	35.7±0.7	36.9±0.8*	36.8±0.4*
$PaCO_2$ (mmHg)	38±4	41±5	41±7
Hemoglobin (gm/dl)	12.9±1.2	8.5±1.2*	9.0±1.2*

* $p < 0.05$ vs (1), mean ± S.D.

Title: THE NEUROMUSCULAR PHARMACOLOGY OF BW A938U DURING ISOFLURANE ANESTHESIA

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Introduction. BW A938U is a new non-depolarizing neuromuscular blocking drug developed by Dr. J. Savarese and Wellcome Research Laboratory. In a previous study BW 938A was reported to be a long-acting non-depolarizing neuromuscular blocking drug with no cardiovascular side effects. This study examined the neuromuscular and cardiovascular effects of this drug during isoflurane anesthesia in patients undergoing surgical procedures.

Methods. 3 groups of patients, each group consisting of 9, ASA class I or II of either sex (excluding females of child-bearing potential), aged 18-59 yrs were studied after institutionally approved informed consent was obtained. Patients were premedicated with morphine (0.10-0.15 mg/kg^{-1}) and atropine (0.004-0.008 mg/kg^{-1}) 45-60 mins prior to induction of anesthesia. Anesthesia was induced with thiopental 4-10 mg/kg^{-1} and maintained with 70% N_2O and isoflurane (0.7% end tidal) for 15 min (Perkin Elmer mass spec). The twitch response of the adductor pollicis muscle to ulnar nerve stimulation was elicited by supramaximal square wave pulses of 0.2 msec duration at a frequency of 0.15 Hz quantitated by an FT10 transducer. After stabilization of the twitch response, one of three doses (7.5, 10.0, and 12.5 µg/kg) of BW A938U was administered as an i.v. bolus over 5-10 secs. The following values were obtained from the analysis of twitch recording: onset time from injection to maximal block, magnitude of maximal block, duration of block from injection to first discernible recovery, and duration of block from injection to 25, 50, 75, and 95% recovery. Heart rate (HR) by ECG and blood pressure (BP) by Dinamap were monitored in all patients. Data was analyzed by linear regression and compared to previous data under nitrous/narcotic anesthesia.

Results. The ED25, 50, 75, and 95 under isoflurane anesthesia obtained from log probit dose response curve were 6.5, 8.6, 11.3, 16.2 µg/kg^{-1} compared to previously published data for nitrous/narcotic anesthesia where ED25, 50, 75, 95 were 10.5, 13, 16, and 23 µg/kg (Fig. 1). The time to maximal block was inversely related to dose. The onset time to maximum block, duration of max block, and recovery data are shown in Table 1. No clinical significant changes were noted in HR, BP, or rhythm.

Discussion. The neuromuscular blocking action of BW A938U was potentiated by isoflurane, an inhalation anesthetic.

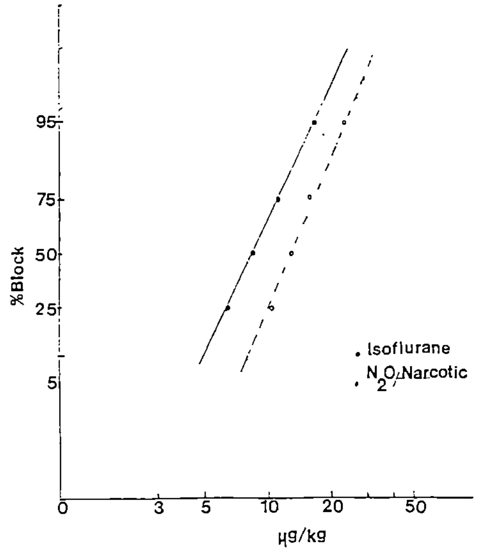

Fig. 1. Log probit dose response curve of BW A938U under isoflurane (•) and nitrous/narcotic (o) anesthesia.

Dose µg/kg	Percent Maximum Block	Onset to Maximum Block (mins)	Time (in mins) to percent recovery 25%	50%	90%
7.5	22.8±8.1	17.6±1.4	-	-	35.1± 4.1
10.0	56.3±9.6	13.2±0.8		47.8±9.0	72.9±17.1
12.5	80.3±5.2	12.0±0.7	32±2.9	46.1±8.2	70.5±15.2

Table 1. Percent maximum block, onset time to maximum block, and recovery of twitch following BW A938U during isoflurane anesthesia. Results are mean ± standard deviation.

Title: FLUID REPLACEMENT: CARDIOVASCULAR RESPONSES IN INFANTS DURING HALOTHANE AND ISOFLURANE ANESTHESIA

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Introduction. During isoflurane and halothane anesthesia in infants, the hypotension that occurs results primarily from changes in the determinants of cardiac function; however, fluid deficits created by the fasting period prior to anesthesia induction may also contribute to this hypotension.[1,2] Using non-invasive pulsed doppler echocardiography to measure left ventricular volumes and pulmonary artery blood flow,[3,4] the cardiovascular effects produced by fluid replacement was studied in infants during equal MAC levels of halothane and isoflurane anesthesia.

Methods. Informed written parental consent was obtained to study twenty healthy (9 d - 32 mo) infants who required elective surgery. These unmedicated infants, who were NPO for four to eight hours preoperatively, were randomly assigned to receive a mask induction via a semiclosed circle of either halothane (n=10) or isoflurane (n=10) in oxygen. After induction, intravenous access was secured, and ventilation controlled with end tidal halothane or isoflurane measured (Beckman LBII). Anesthesia was maintained at 1.25 MAC halothane or isoflurane (adjusted for age)[5,6] for five minutes (25-30 minutes following induction) and then the cardiovascular data was collected. Immediately following this measurement, with anesthesia maintained at 1.25 MAC, 15 ml/kg of Lactated Ringers (LR) was infused and the cardiovascular measurements were repeated. The cardiovascular data included blood pressure, heart rate by EKG and pulsed doppler echocardiography to measure left ventricular area at the level of the papillary muscle, left ventricular length and mean pulmonary artery velocity. Left ventricular end diastolic volume (LVEDV), cardiac index (CI), stroke volume index (SVI), and ejection fraction (EF) were derived from the pulsed doppler echocardiographic data. Results were analyzed using a two-way analysis of variance. Significance was accepted at $p<0.05$.

Results. Mean blood pressure (MBP) was similar in the halothane and isoflurane groups before fluid; however, infants who received isoflurane had higher heart rates both before and after fluid than infants who received halothane (Table 1). After Lactated Ringers, blood pressure decreased significantly in the isoflurane group, but was unchanged in the infants who received halothane (Table 1). LVEDV increased significantly following fluid administration in both groups of infants (Figure 1a). The EF and SVI decreased significantly after LR in the halothane group, but increased after LR in patients who received isoflurane (Figures 1b,1c). CI decreased in infants who received halothane, but increased in patients who received isoflurane after the fluid (Figure 1d).

Discussion. An increase in LVEDV (preload) improves cardiac contractile performance and increases stroke volume and cardiac output in the normal heart (Starling's law of the heart).[7] This intrinsic myocardial property was examined in these infants by increasing preload with 15 ml/kg of Lactated Ringers. In the infants who received isoflurane, improvements occur in EF and SVI suggesting this response is maintained, while in patients who received halothane, ejection fraction and stroke volume index decreased, suggesting halothane anesthesia may impair myocardial responses to increased LVEDV in infants. This difference in response to increased preload between isoflurane and halothane may be important in clinical practice. Changes in cardiac performance by halothane and isoflurane are more important causes of hypotension than fluid deficits.

Table 1. Changes in MBP and HR

	Before Fluid	After 15 ml/kg LR
HR (beats/min)		
Halothane	119.4±3.5	123±2.6
Isoflurane	142.7±6.7+	135±7.5+
MBP (mmHg)		
Halothane	58.9±2.9	57.9±2.4
Isoflurane	60.6±3.1	49.5±3.1+*

+p<0.05 from Halothane, *p<0.05 from before fluid

References.

1. Wolf WJ, et al. Anesthesiology 64:328, 1986.
2. Diaz JH, Lockhart CH. Anesthesiology 51:S313, 1979.
3. Mercier JC, et al. Circulation 65:962, 1982.
4. Pearlman AS, et al. Am J Cardiol 46:1256, 1980.
5. Gregory GA, et al. Anesthesiology 30:488, 1969.
6. Cameron CB, et al. Anest Analg 63:418, 1984.
7. Gleason WL, Braunwald E. Circulation 25:841, 1962.

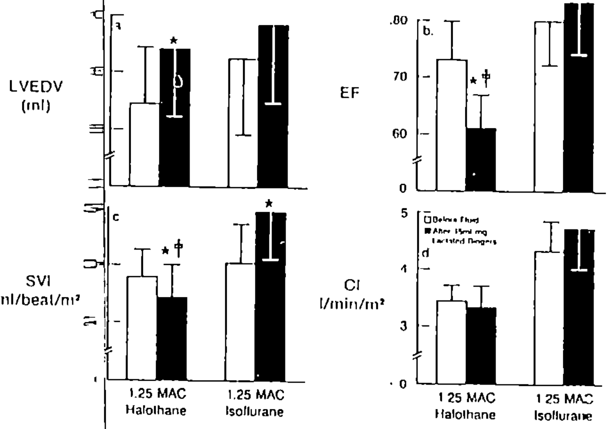

FIGURE 1: Cardiovascular measures before and after 15ml/kg Lactated Ringer's
(a) Left Ventricular End Diastolic Volume (LVEDV)
(b) Ejection Fraction (EF)
(c) Stroke Volume Index (SVI)
(d) Cardiac Index (CI)

(*p<0.05 from before fluid, ǂp<0.05 from isoflurane)
Values expressed as mean and SEM

White box = Before Fluid
■ Black box = After 15 ml/kg Lactated Ringers

Title: THE NEUROMUSCULAR EFFECTS OF PIPECURONIUM UNDER ENFLURANE ANESTHESIA

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Introduction Pipecuronium bromide (Arduan) is a bisquaternary, nondepolarizing muscle relaxant (MR) undergoing clinical pharmacological investigation in the U.S.A. In patients who received balanced anesthesia it was about 40% more potent than vecuronium, the duration of its neuromuscular (NM) effect was similar to that of pancuronium, but unlike pancuronium it did not increase heart rate (HR) or blood pressure (BP). In the present study, the NM effects of pipecuronium were investigated in patients receiving enflurane anesthesia.

Methods This study, approved by the Institutional Review Board, was carried out on 30 patients of either sex (ASA classification I and II) who signed informed consents. After premedication with i.m. diphenhydramine meperidine, anesthesia was induced with 3 - 5 mg/kg thiopental followed by the inhalation of 3 liter/min N_2O - 2 liter/min O_2 containing 3% enflurane during the first 5 min and 2% thereafter. The isometric force of contraction of the adductor pollicis muscle elicited indirectly by trains of four (TOF) 2Hz supramaximal square wave impulses of 0.2 ms duration, administered every 10s, was quantitated by FT10 transducers and continuously recorded. When T1 (the response to the first of the TOF impulses) became stable an initial dose of 10 μg/kg pipecuronium was injected i.v. Subsequently, depending on the response to the first dose, 2.5 to 10 μg/kg increments were administered, whenever the response to the preceeding dose became maximal, until > 90% block developed. At this time patients were intubated. From the log dose-response regression line the ED50 and ED90 of pipecuronium was determined for each patient. Subsequently the concentration of enflurane was adjusted to maintain adequate anesthesia. When necessary 12 μg/kg pipecuronium was administered for maintenance of surgical relaxation, whenever T1 recovered to 25% of control. If at the termination of anesthesia the T4/T1 ratio was < 0.75 the residual NM block was antagonized by the i.v. injection of a mixture of 40 μg/kg neostigmine and 15 μg/kg atropine. The NM and circulatory (HR and BP) effects of pipecuronium observed under enflurane anesthesia will be compared with the observations made in an earlier study in patients under balanced anesthesia.

Results The data of table 1 indicate that the NM potency of pipecuronium was about 1.5 times greater under enflurane than under balanced anesthesia. The total dose of pipecuronium required to decrease T1 to < 10% of control was 30.0 ± 1.1 μg/kg (Mean ± SEM) under enflurane and 43.5 ± 2.1 μg/kg under balanced anesthesia. Complete NM block developed in 24 and 13 patients in the enflurane and balanced anesthesia groups respectively. The time for the return from the first visible T1 to 25% of control was about 50% longer in the enflurane than in the balanced anesthesia group . The mean clinical duration of 12 μg/kg repeat doses of pipecuronium were longer under enflurane than those of 15 μg/kg doses under balanced anesthesia. In comparison to the recovery of T1 the T4/T1 ratio increased more rapidly after reversal in the enflurane than in the balanced anesthesia group (see Table 2). The amount of pipecuronium used for the dose-response determination had no effect on HR and BP in the enflurane group, but decreased HR by about 8%, without affecting BP, in the balanced anesthesia group.

Discussion As is the case with other nondepolarizing MR, enflurane significantly increased the potency and duration of action of pipecuronium. After reversal with neostigmine T1 only returned to about 75% of its control value. In contrast T4/T1 ratio was 0.88 at this time, indicating that under enflurane anesthesia, after reversal with neostigmine, NM transmission recovers more completely than the force of contraction of the muscle. This observation is compatible with results of animal experiments[2] which indicated that enflurane depresses the contractility of the muscle fiber, but has little or no effect on NM transmission. The myoneural effect of enflurane is long lasting and can be reversed by 4-aminopyridine but not by neostigmine. The findings presented indicate that after the combined administration of enflurane and pipecuronium, even after satisfactory reversal (T4/T1 ratio = 0.88) of NM transmission by neostigmine, muscle strength does not return to its control value.

Table 1. The neuromuscular effects of pipecuronium under enflurane and balanced anesthesia

	Enflurane	Balanced	P < *
ED 50 (μg/kg)	13.3±0.7(29)†	20.3±1.1(30)	0.001
ED 90 (μg/kg)	22.2±1.0(29)	33.0±1.6(30)	0.001
Recovery (min) of T1 from 1 to 25%	45.6±5.5(24)	31.9±6.9(13)	ns
Maintenance Dose (μg/kg)	12	15	
Duration (min)			
1st dose	58.1±4.2(18)	41.3±2.9(21)	0.01
2nd dose	50.2±6.3(5)	52.5±5.4(13)	ns

* Indicates significance of difference between enflurane and balanced anesthesia groups (Student's t test).

† All values are Means ± SEM of number of cases indicated in parenthesis.

Table 2. Reversal of the pipecuronium induced neuromuscular block under enflurane and balanced anesthesia

	Enflurane (27)		Balanced (24)	
	T1(% of control)	T4/T1	T1(% of control)	T4/T1
Before Reversal	35.0±2.1†	0.22±0.03	39.7±5.2	0.17±0.05
After Reversal				
2 min	54.9±2.6	0.63±0.03	59.1±5.0	0.49±0.06
5 min	66.9±2.7	0.80±0.02	78.0±4.2	0.70±0.04
10 min	73.8±2.6	0.88±0.01	88.1±3.5	0.83±0.02

Meaning of symbols as indicated in table 1.

References 1. Foldes FF, Nagashima H, Nguyen HD, et al: The human cumulative dose-response of pipecuronium bromide under balanced anesthesia. Anesthesiology 65, September, 1986
2. Ohta Y, Nagashima H, Lofrumento R, et al: Halothane-isoflurane interactions in vivo. Anesthesiology 53:S265, 1980

Title: INACTIVATION PATHWAYS OF ATRACURIUM: EVIDENCE FOR AN ADDITIONAL ROUTE

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Introduction. Hofmann elimination and ester hydrolysis have been described as the two pathways of inactivation of atracurium (A). Generation of laudanosine in vivo and in vitro has been cited as evidence in support of Hofmann elimination. Ester hydrolysis was reported to be catalyzed by enzymes in plasma. Supporting evidence was recently provided by the demonstration of an inhibitory effect of organophosphorous compounds on the inactivation of A. Whereas the notion of enzyme-catalyzed hydrolysis of A seems adequately documented, the presence of laudanosine in the incubation solution or in plasma in vivo cannot be accepted as sufficient proof that laudanosine was generated exclusively by Hofmann elimination. Chemically, a nucleophilic substitution reaction (SN2) is an alternative inactivation pathway that also yields laudanosine as an end-product. We hypothesized that the SN2 reaction may become evident if, at the same pH and temperature, the in vitro inactivation of A proceeds faster in the presence of a nucleophile. Propionic acid and its derivatives (alanine and cysteine) were selected as test substances to be added to the incubation solution (saline). Metocurine (M) was substituted for A in some experiments to test whether the incubation with cysteine causes spurious interference with the neuromuscular block produced by non-depolarizing relaxants.

Methods. Incubations of A were carried out in 0.9% NaCl solution at 37°C. Sodium propionate, alanine, or cysteine (0.1 M) were added when required. The solutions were brought to pH 7.4 before the addition of A (1 mg/ml; total incubation volume 10 ml). A pH electrode was used to monitor the activity of hydrogen ions during the incubations. Small amounts of sodium hydroxide were used if necessary for the maintenance of constant pH (7.4). Before and during the incubations with cysteine the solutions were deoxygenated with humidified nitrogen. M (0.02 mg/ml) was similarly incubated in saline with or without the addition of cysteine (0.1 M).

Aliquots of the incubation solutions were collected as soon as possible after the addition of the relaxants (0 min incubation) and again after 45 min of incubation and immediately administered intravenously to anesthetized rats. When the aliquots contained A, the second aliquot was injected into the same animal; when M was present, a freshly prepared rat was used (to exclude cumulative effects). Initially the dose of A was 2.4 mg/kg and that of M 0.025 mg/kg. A force transducer and a polygraph were used to record the onset and duration of relaxation, the magnitude of the neuromuscular block, and the rate of recovery of the indirectly stimulated m. gastrocnemius. Single supramaximal, square-wave stimuli (0.2 Hz, 0.2 msec duration) were applied to the transected, ipsilateral sciatic nerve. The twitch height after the administration of the relaxants was expressed in percent of the respective preinjection values. Each incubation setting was repeated four times with A and twice with M. All data were subjected to analysis of variance.

Results. The first injections of aliquots containing A (0 min incubation) produced a complete muscle paralysis that was independent of the additives present. After 45 min of incubation, the neuromuscular block was still complete if the incubation was carried out in plain saline or in saline containing sodium propionate. Inactivation of A was manifested, however, by shorter duration of relaxation. Incubation with alanine resulted in a just discernible decrease of the block and markedly shortened duration of relaxation. By contrast, no block, or only a minimal block, was evident when cysteine was present during incubation. Neuromuscular block produced by M was not influenced by incubation with or without cysteine.

Discussion. The data show that the "spontaneous" inactivation of A is not only dependent on temperature and pH of the incubation solution but also on its composition. Although pH and temperature were maintained constant, the presence of alanine (α-amino propionic acid) and, more significantly, of cysteine (α-amino, β-mercapto propionic acid) facilitated the inactivation of A. Our experiments do not provide information about the nature of the products formed when alanine or cysteine were present in the incubation solutions. Among other alternatives, the possibility has to be considered that cysteine might have inactivated A by a direct attack on the parent molecule in a nucleophilic substitution reaction (SN2). It remains to be explored whether this reaction may contribute to the inactivation of A under in vivo conditions.

Influence of Additives to the Incubation Solution on the Inactivation of Atracurium at pH 7.4 and 37°C
(n=4; mean ± SEM)

Additive	Duration of incubation (min)	Duration of the N-M block (sec)	Magnitude (%)
0	0	294±7	100[a]
	45	202±32	99.7±0.3
Na-propionate (0.1M)	0	273±46	100[a]
	45	220±34	99.5±0.3
Alanine (0.1M)	0	251±10	100[a]
	45	120±15	96.0±0.6
Cysteine (0.1M)	0	215±16	99.7±0.3
	45	c	0;0;0;11[b]

[a] Complete relaxation produced in all four rats.

[b] Individual data

[c] Could not be determined

V.N. is a recipient of the B.B. Sankey Anesthesia Advancement Award 1986 from IARS. The Award is gratefully acknowledged.

Title: PROTAMINE REQUIREMENT FOLLOWING CARDIOPULMONARY BYPASS IN CHILDREN

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Introduction. The protocol for protamine administration to neutralize heparin anticoagulation after cardiopulmonary bypass (CPB) varies greatly. Many investigators[1,2,3] have attempted to determine a minimum effective dose of protamine to avoid the possible deleterious cardiovascular effects related to protamine administration. While the dose-response curve obtained from the activated coagulation time (ACT) has been widely employed, its use has not been validated in children. Consequently, we determined the minimum effective dose of protamine in pediatric patients undergoing CPB and compared it to the calculated dose derived from the pre-bypass ACT dose-response curve for heparin.

Methods. Eighteen patients (n=18) undergoing surgery with CPB for repair of congenital cardiac anomalies were studied under an institutionally approved protocol. Anesthesia was induced and maintained with nitrous oxide, oxygen, pancuronium, and halothane or narcotics. Anticoagulation by heparin was assessed with the Hemochron^R device according to the following scheme. After a baseline ACT measurement, heparin 400 units/kg was administered with the goal of achieving an ACT value of 450 sec or greater. Additional heparin was administered as required to maintain the ACT above 450 sec. At the successful completion of CPB, the ACT was measured and the required dose of protamine was calculated from the dose-response curve determined pre-bypass.[1] For neutralization of heparin, we initially administered protamine 1 mg/kg via peripheral i.v. and determined the ACT after 3-5 min. A second dose of protamine 1 mg/kg was then given, with additional doses (1 mg/kg) as required to return the ACT to baseline. A retrospective control group of 26 children (n=26) who underwent repair of congenital cardiac defects employing CPB were used for comparison. These 26 consecutive patients underwent surgery prior to the initiation of the above experimental study protocol and received a dose of protamine calculated according to the dose-response curve for heparin. Protamine, 1.3 mg, was administered for each 100 units of heparin calculated to be circulating in the patient. The demographic characteristic of each group was compared. Data were reported as mean ± SEM. Statistical analysis was performed using analysis of variance and Student's t test. $P \leq 0.05$ was considered significant.

Results. In the experimental study group, the age was 4.2 ± 1.03 yr (range 2d-10 yr), weight 17.3 kg. No patient received more than 2 mg/kg of protamine despite calculated dose 4.7 ± 0.16 mg/kg to return the ACT to baseline level. In the control group, the age was 2.9 ± 0.67 yr (range 3d-13 yr), weight 12.3 kg. All received 4.9 ± 0.11 mg/kg of protamine and the ACT returned to baseline (table). No significant differences existed between groups in terms of the baseline ACT and post-protamine ACT values as well as age, weight, and bypass time. No patients received additional protamine for excessive postoperative bleeding in the ICU.

Discussion. Different methods are used to determine the dose of protamine required to reverse heparin activity after CPB. The heparin-ACT dose response curve is widely used although it has not been validated in pediatric patients. Under the conditions of this study, administration of protamine (1 mg/kg) could reduce an average ACT to 165 sec; however, clinically, this ACT was considered still prolonged as compared to the baseline despite insignificant statistical differences. An additional dose of protamine (1 mg/kg) therefore was given to provide a margin of safety and did reduce the ACT to baseline level in all patients. Thus, the total dose of protamine could be reduced approximately 43% (4.7 mg vs. 2.0 mg) of the estimated dose.

Table. ACT in baseline, before and after reversal of heparin anticoagulation.

		CONTROL (N=26)	STUDY (N-18)	P
baseline (sec)		120 ± 2.7*	119 ± 2.6*	(NS)
p heparin (400 u/kg)		529 ± 19.8	537 ± 23.7	(NS)
p CPB		548 ± 13.7	528 ± 14.5	(NS)
1.0	mg/kg	—	165 ± 14.6*	
2.0	protamine		116 ± 2.6*	
4.9		123 ± 4.3*	—	* NS

NS: non-significant

References.

1. Bull BS, Huse WN, Brauser FS, et al: Heparin therapy during extracorporeal circulation: II. The use of a dose-response curve to individualize heparin and protamine dosage. J Thor Cardiovasc Surg 69:685-689, 1975
2. Dutton DA, Hothersall AP, McLaren AD, et al: Protamine titration after cardiopulmonary bypass. Anaesthesia 38:264-268, 1983.
3. Umlas J, Taff RH, Gauvin G, et al: Anticoagulant monitoring and neutralization during open heart surgery -- a rapid method for measuring heparin and calculating safe reduced protamine doses. Anesth Analg 62:1095-1099, 1983

Title:

LIDOCAINE PREVENTS LOSS OF CEREBRAL BLOOD FLOW AUTOREGULATION AFTER ASPHYXIA IN NEWBORN LAMBS

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Introduction. Neonatal asphyxia can impair autoregulation of cerebral circulation. In preterm neonates, loss of autoregulation allows cerebral blood flow (CBF) to vary with fluctuations in arterial blood pressure and may lead to intracranial hemorrhage, central nervous system damage or death[1]. Lidocaine has been reported to have protective effects in acute cerebral ischemia induced by air embolism[2]. Therefore, we assessed the effects of lidocaine on CBF and its autoregulation after a period of asphyxia in newborn lambs.

Methods. Thirteen 1-3 day old lambs were anesthetized with 70% N_2O, 30% O_2 and paralyzed with d-tubocurarine. The skin of their groin and neck was anesthetized with 1% lidocaine for insertion of catheters into the femoral artery, and vein as well as lingual artery. ^{133}Xenon was injected through the lingual artery and xenon washout from the brain was measured with a gamma counter placed over the right parietal area. CBF was derived from the initial slope of the xenon washout curve. CBF autoregulation was assessed by determining CBF at resting, elevated and decreased mean arterial blood pressures (MAP) before asphyxia and after asphyxia. MAP was increased by infusion of 0.02% phenylephine and decreased by infusion of 0.1% sodium nitroprusside solutions. After surgical preparation, the lambs were allowed to recover for 2 hours. After stabilization and demonstration of normal CBF autoregulation, 6 lambs received lidocaine 5 mg/kg by intravenous infusion over 5 minutes. All the lambs were then subjected to 30 minutes of asphyxia (P_aO_2 15-32 mmHg, $PaCO_2$ 50-76 mmHg). After asphyxia, all lambs were maintained at normoxia and normocapnia for the duration of studies. Lidocaine concentrations were determined by gas liquid chromatography with a nitrogen-specific detector. Data were compared by analysis of variance and presented as mean ± SEM.

Results. The CBF data are presented in the table. The plasma lidocaine concentration in the lidocaine-treated lambs was 3.5 ± 0.4 ug/ml at the beginning of the asphyxia period. During asphyxia, CBF increased significantly in all the lambs. The increases in the untreated lambs were greater than those in the lidocaine-treated lambs. In the untreated lambs, at 30 and 90 minutes after the end of asphyxia, CBF increased with MAP elevation and at 30 minutes after asphyxia, CBF decreased with MAP reduction. These changes indicate impairment of CBF autoregulation in the untreated lambs. After termination of asphyxia, the lidocaine-treated lambs maintained fairly constant CBF during increases and decreases in systemic blood pressure, indicating normal autoregulation. CBF at resting MAP decreased after asphyxia in both groups, but the decrease in CBF of untreated lambs occurred later, being significant only at 90 minutes after the asphyxia period.

Discussion. These results confirm our previous studies which showed impairment of CBF autoregulation after asphyxial stress in newborn lambs. The lidocaine-treated lambs maintained normal autoregulation after asphyxia but had a decreased level of cerebral perfusion. The CBF reduction may be caused by a decrease in cerebral metabolic rate which has been reported in adult dogs[3]. The protective effects of lidocaine may be related to a decrease in cerebral metabolic rate or the membrane-stabilizing effect of lidocaine. Further experiments are needed to determine the mechanism of action. Clinically, if the observed protective effects of lidocaine against acute asphyxia can be confirmed in human neonates, lidocaine may be considered the anesthetic agent of choice for mothers with compromised infants.

References.

1. Lou HC, Lassen NA, Friis-Hannen B: Impaired autoregulation of cerebral blood flow in the distressed newborn infant, J Pediatr 1979;94:119-121.
2. Evans DE, Kobrin AI, LeGrys DC, Bradley ME. Protective effects of lidocaine in acute cerebral ischemia induced by air embolism. J Neurosurg. 1984;60:257-263.
3. Sakabe T, Maekawa T, Ishikawa T, Takeshita H. The effects of lidocaine on canine cerebral metabolism and circulation related to the electroencephalogram. Anesthesiology 1974;40:433-441.

CBF(ml/100g/min)

	Untreated lambs	Lidocaine-treated lambs
Before asphyxia		
Decreased MAP	60 ± 3	63 ± 4
Resting MAP	63 ± 3	66 ± 4
Elevated MAP	63 ± 3	66 ± 4
During asphyxia		
Resting MAP	206 ± 8**	138 ± 17**
30 min after asphyxia		
Decreased MAP	53 ± 3#	53 ± 2
Resting MAP	61 ± 5	53 ± 2*
Elevated MAP	73 ± 6##	53 ± 2
90 min after asphyxia		
Decreased MAP	51 ± 3	47 ± 1
Resting MAP	52 ± 2*	49 ± 1*
Elevated MAP	58 ± 3#	49 ± 1

*P < 0.05; **P < 0.01 compared to CBF at resting MAP before asphyxia
#P < 0.05; ##P < 0.01 compared to CBF at resting MAP at the same time period

Title : A NEW FIBEROPTIC INTUBATING AIRWAY

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INTRODUCTION: In anesthetized patients fiberoptic orotracheal intubation (FOI) often is difficult because relaxation of the oropharyngeal tissues and tongue leave little air space at the oropharynx for maneuvering the distal end of the fiberscope and to keep the tip of the fiberscope away from the tissues. To overcome this problem a new intubating airway was designed and tried in both awake and anesthetized patients.

DESCRIPTION OF THE AIRWAY: The fiberoptic intubating airway is designed to accomodate an endotracheal tube while being directed to the trachea with the help of a fiberscope. The airway has a flat lingual surface on the proximal half which minimizes movement of the airway. The distal portion of the airway curves about 90% away from its proximal end and tapers towards its distal edge. The wide distal portion of the airway prevents the tongue and soft tissues of the anterior pharyngeal wall from falling back and obstructing the view of the epiglottis and larynx. The airway has a tubular passageway on its proximal portion to permit passage of a tracheal tube. This tubular section is capable of being opened at the top, permitting the airway to be removed from the patient's mouth (Fig.1).

MATERIALS AND METHODS: After approval by Institutional Review Board, patients scheduled for surgical procedures under endotracheal general anesthesia were included in this study. During the preoperative visit the details of the procedure was explained and consent was obtained from each patient. A total of 34 intubations were performed in 32 men and 2 women. Ninteen intubations were performed in anesthetized and paralyzed patients and 15 in awake and sedated patients. For awake FOI, sedation is achieved by intravenous titration of diazepam and fentanyl. After application of topical anesthesia to the oropharynx, fiberoptic intubating airway is placed in the mouth. The lubricated tracheal tube is placed inside the airway intubator, and fiberscope is passed through tracheal tube into the oropharynx for glottis exposure. Topical anesthesia of larynx and trachea is achieved either by spraying of local anesthesia through channel of fiberscope or by translaryngeal injection of 3 ml of 4% xylocaine. After vocal cords exposure, the fiberscope is advanced into the trachea. The tracheal tube is then threaded over the fiberscope and through the airway into the trachea. For intubation in anesthetized patients, after general anesthesia and muscle relaxation is established, the mask is removed and intubating airway is placed inside the mouth. The oropharynx is suctioned and mask ventilation is resumed and continued for 30-60 seconds. The mask is then removed, fiberscope fitted with tracheal tube is inserted through the airway and the vocal cords into the mid trachea. The tracheal tube is then threaded over the fiberscope through the airway and into the trachea.

RESULTS: The airway was tolerated well by all 15 awake patients. Visualization of vocal cords was considered easy in 12 and moderately difficult in 3 cases. Intubation was successful on first attempt in 14 patients, and on second attempt in one. In 5 cases advancement of tube was encountered with resistance, which was overcome vy pulling the tube back and readvancing by giving 90°-180° rotations to the endotracheal tube. Average intubation time was 1.3 min. (range 0.3-6 mins.). In 18 anesthetized patients intubation was achieved on the first attempt, in one on the second attempt. Visualization of the vocal cord was considered easy in all 19 cases. In 17 occassions the tracheal tube entered the trachea smoothly on the first try. On 2 occasions it met resistance which was overcome by method stated above. Average Intubation time was 20 seconds (range 15-25 sec.). There was no trauma to upper airway soft tissues.

DISCUSSION: The fiberoptic intubating airway provides the conditions for safe and easy FOI in both awake and anesthetized patients. Because of the shape of the airway and because the tongue is retracted anteriorly, adequate open space is provide for easy manipulation of the fiberscope and for easy exposure of the epiglottis and the vocal cords. Patients tolerance and acceptance of awake FOI by this approach is extremely good and the cardiovascular response to laryngoscopy and tracheal intubation is minimal. It isconcluded that the new intubating airway facilitates the FOI in both awake and anesthetized patients.

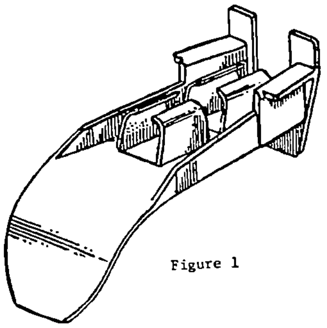

Figure 1

Title: COMPARISON OF EPIDURAL BUTORPHANOL AND MORPHINE FOR ANALGESIA CESAREAN SECTION

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Introduction. The efficacy of epidural opiates for the relief of pain following Cesarean section is well established. Five milligrams of epidural morphine provides good to excellent analgesia for a duration of 24 to 36 hours[1]. Morphine, a pure opioid agonist, primarily activates mu receptors which mediate not only effective analgesia but also undesirable side effects such as respiratory depression, pruritis, urinary retention and sedation. In addition, respiratory depression secondary to rostral spread of the poorly lipid soluble morphine requires prolonged monitoring of cardiovascular and respiratory parameters. Butorphanol, a more lipid soluble agonist antagonist, has been shown to provide rapid analgesia following Cesarean section when administered epidurally, with minimal side effects[2].

To confirm the efficacy of epidural butorphanol versus morphine for pain relief following Cesarean section, we conducted a double blind randomized dose response study of three doses of 1, 2, or 4 milligrams of butorphanol and 1 dose of 5 milligrams of morphine.

Methods. Following approval from the committee on human research and obtaining a written informed consent, 92 ASA class I-II patients who had selected epidural anesthesia for Cesarean section were evaluated. T4 levels of anesthesia were established by 2% lidocaine with 1:200,000 epinephrine. With the onset of postoperative pain, patients were randomly assigned to receive a single epidural dose of either 1, 2, or 4 milligrams of butorphanol or 5 milligrams of morphine diluted in normal saline to a total volume of 10cc. Pain intensity and pain relief were evaluated using a 10cm visuolinear scale at specified intervals. Vital signs and the incidence of side effects were also recorded. Statistical analysis of data was by analysis of variance with Duncan's Multiple Range Test. P<0.05 was considered significant.

Results. The characteristics of the four groups were not statistically different in terms of age, height, weight, or primary section versus repeat section. Initial pain intensities were not statistically different in the 4 groups with a mean pain intensity score of 6.4. The 3 groups of butorphanol provided rapid and excellent pain relief within 15 minutes as compared to morphine which is associated with a statistically significant mean onset time of 30 minutes. The 3 groups of butorphanol continued to provide excellent analgesia throughout the initial 1 hour. During the second and third hour, there was no significant difference among the four groups. Morphine did not begin to provide significantly greater pain relief until 4 hours. Four milligrams of butorphanol was associated with the longest mean duration of action of 5.3 hours among the 3 groups of butorphanol. Although morphine was associated with a significant duration of action of 15.8 hours, the 4 milligram butorphanol group received the highest patient global assessment rating of 3.6. Cardiovascular and respiratory stability were maintained in all 4 groups. Pruritis was the only adverse side effect, with a 40% incidence in the morphine group versus 4% in the butorphanol group. (Table 1)

Discussion. Epidural butorphanol provided effective analgesia within 15 minutes for a mean duration of 4.6 hours without a significant incidence of side effects. Four milligrams of butorphanol provided effective analgesia for a mean duration of 5.3 hours. In eight patients 4 milligrams butorphanol provided analgesia for up to 6 - 20 hours. Four milligrams of butorphanol received the highest score in terms of patient global assessment despite the prolonged duration of action in the morphine group. Epidural butorphanol appears to be an efficacious alternative to morphine for analgesia following Cesarean section.

References.

1. Kotelko DM, et al. Epidural morphine analgesia after cesarean section delivery. Obstet Gynecol 1984;63:409.
2. Naulty SJ, et al. Epidural butorphanol for analgesia following cesarean delivery (abstract). SOAP 1984;27.

Table 1.

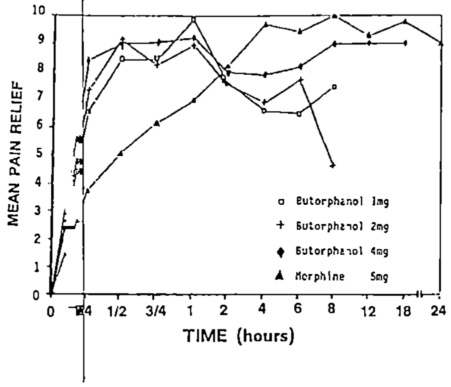
	B1	B2	B4	M5
Initial Pain Intensity: (Scale -10)	5.7	6.4	6.8	6.7
Time Pain Half Gone: (Hour)	.28	.33	.21	.5*
Relief 15 Minutes: (Scale 0-10)	6.6*	7.4*	8.4*	3.7
Relief 1 Hour: (Scale 0-10)	9.9*	9.0*	9.2*	7.0
Relief 4 Hours: (Scale 0-10)	6.6	6.9	7.9	9.7*
Time to Remedicate: (Hour)	4.4	4.1	5.3	15.8*
Pruritus:	4%	-	-	43%*
Patient Global Assessment: (Scale 0-5)	3.0	2.8	3.6	3.3

n=[illegible]/group

B1=Butorphanol 1mg
B2=Butorphanol 2mg
* [illegible] 0.05

B4=Butorphanol 4mg
M5=Morphine 5mg

MEAN PAIN RELIEF SCORES



Title: COMPARATIVE HYPOTENSIVE RESPONSES OF THE CARBONATED AND HYDROCHLORIDE SALTS OF LIDOCAINE IN EPIDURAL BLOCKS

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Introduction Epidural anesthesia with its slower and more predictable onset of action has become increasingly preferred over sub-arachnoid blocks for caesarean sections. A major disadvantage of spinal anesthesia is a marked fall in cardiac output and blood pressure (BP) resulting from rapid onset of high sympathetic block.

The onset and adequacy of epidural anesthesia have been shown to be significantly improved by use of the carbonated salts of lidocaine and epinephrine (E),[1,2] secondary to the higher pH of the carbonated solutions requiring less buffering, and facilitating liberation of free base which diffuses rapidly into the nerve fibers. This study was undertaken to determine whether carbonated lidocaine +E with its shortened latency period also has a more pronounced effect on BP as compared to the non-carbonated (hydrochloride) salts.

Methods Twenty-one ASA I-II full term gravida patients undergoing elective C-section were studied using a randomized double-blind design. The protocol was approved by the Institutional Review Board for Human Research. All patients were hydrated with 1.5-2.0 liters of Ringers lactate. An epidural catheter was placed in the sitting position after the injection of 18 cc of local anesthetic. The patient was placed supine with a wedge under the right hip to achieve left uterine displacement. Local anesthetic was given, if necessary, to obtain a T_4 level. One group (n=11) received 2% lidocaine with epinephrine 1:200,000 and the other group (n=10) received the same but with 1 meq of $NaHCO_3$ per 10 cc of local anesthetic added just prior to injection. Blood pressure was then measured every minute for twenty minutes. Patients were treated for hypotension with ephedrine at the discretion of the anesthetist. BP differences between groups were tested for statistical significance (P<.05) by use of the t-test.

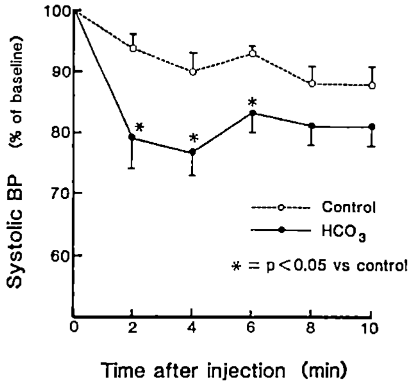
Results BP data from the patients in this study are tabulated below:

	BASELINE VALUE (MM HG)	LOWEST VALUE (MM HG)	MAXIMUM DECREASE (%)	RATE OF DECREASE (%/MIN)
SYST. BP				
HCO_3	137 ± 4	94 ± 5*	32 ± 3*	9 ± 1*
CONTROL	137 ± 4	111 ± 4	19 ± 3	3 ± 1
DIAST. BP				
HCO_3	77 ± 1	46 ± 4	39 ± 6	9 ± 3
CONTROL	75 ± 3	51 ± 3	31 ± 5	4 ± 1

*P<.05 VS CONTROL

The HCO_3 and control groups of patients did not differ in baseline values for either systolic or diastolic BP. Furthermore, both groups showed significant maximum declines from both systolic and diastolic BP baselines whether expressed in absolute value or as a % of baseline value. Whereas decreases in diastolic BP were not different between HCO_3 and control groups, HCO_3-treated patients showed maximum decreases in systolic BP which were larger and more rapid than those in control patients.

Differences in systolic BP changes between HCO_3 and control groups are detailed further in the figure:



When systolic BP values are plotted at 2-min intervals after anesthetic administration, the more rapid decline to lower values in HCO_3-treated patients is readily seen. Differences in systolic BP are significant at 2,4 and 6 min but not thereafter, due to a continuing BP decline in the control group and also to a rise in the HCO_3 group. Six of 10 HCO_3 patients received ephedrine at an average total dose of 21 mg (upper limit 55 mg), whereas 3 of 11 controls received an average total dose of 12 mg ephedrine (upper limit 20 mg).

Discussion Despite the preliminary nature of this study's findings, significantly greater magnitudes and rates of decline in systolic BP were seen with carbonated lidocaine +E as compared to the hydrochloride salt. This difference persisted at 2, 4, and 6 minutes despite the more extensive use of ephedrine in the carbonated group. Differences beyond 6 minutes were not significantly different, perhaps in part due to continued aggressive treatment with ephedrine and volume in the HCO_3 group. This difference is consistent with the finding that onset and adequacy of anesthesia are significantly improved with carbonated lidocaine [1,2]. Hypotension in C-section has been associated with maternal nausea, and in view of the adverse effects of hypotension on utero-placental blood flow, we suggest caution in the use of the carbonated solution. This is especially so in pre-eclamptic or eclamptic patients whose volume-contracted state predisposes them to dramatic hypotension following the sympathectomy of epidural or spinal anesthesia.

References

1. Bromage PR, et al: Quality of epidural blockade. III. Carbonated local anesthetic solutions. Br J Anaesth 1967;39:197-208.
2. Difazio CA, et al: Comparison of pH-adjusted lidocaine solutions for epidural anesthesia. Anesth Analg 1986;65:760-4.

Title: THE EFEECTS OF METOCLOPRAMIDE ON INTRAOCULAR PRESSURE

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Introduction. Metoclopramide is frequently used by some anesthesiologists as a standard premedicant not only for patients undergoing emergency surgery but for patients having elective outpatient surgery. As a gastro-kinetic agent, metoclopramide stimulates the upper gastro-intestinal tract without stimulating gastric secretions, relaxes the pyloric spincter and also the duodenal bulb. The net effect of these actions is to decrease gastric emptying time and to hasten peristalasis. Further, metoclopramide may produce in some patients extrapyramidal symptoms including oculogyric crisis, protrusion of the tongue, torticollis, trismus and dystonic reactions[1]. The effect of metoclopramide on the smooth muscles of the eye and consequently on intraocular pressure (IOP) have not been reported. The purpose of this study is to examine the effect of metoclopramide on IOP perioperatively.

Methods. This study was approved by our institutional review board and informed consent was obtained from all patients. The patients studied were divided into two groups. Group I patients served as controls and IOP measurements were made prior to induction, half a minute after sodium pentothal administration, half minute, one minute, three minutes and five minutes after succinylcholine administration. For Group II (the test group) patients, metoclopramide 10 mg IV was administered 30 minutes prior to induction of anesthesia. IOP measurements were made immediately before and 1, 3, 5, 15 and 30 minutes following metoclopramide administration. Thereafter, IOP was measured following sodium thiopental and succinylcholine administration as described above for the Group I patients. IOP measurements were made using "Jewel" Model Sklar-Schiotz tonometer and topical anesthesia was achieved prior to IOP measurements with two drops of 0.5% alcaine (proparacaine hydrochloride) ophthalmic anesthetic.

Results. Fig. 1 shows the means of the intraocular pressure readings of the control and metoclopramide patients. Standard deviations of the metoclopramide patients were also shown in the test group. A noticeable rise in IOP is shown within 5 min. of metoclopramide administration. An additional rise is evident within 3 min. of succinylcholine administration in the same group of patients and this was greater than the rise observed in the control corresponding patients. These results are not statistically significant (Student's t-test) because of the small number of cases used. However, the results were highly clinically significant.

Discussion. Knowledge of the effect of anesthetic drugs on IOP is important especially in patients with perforated eye injuries. Metoclopramide by virtue of its effect on the gastrointestinal tract and, in particular, on the stomach has been used as part of the anesthetic regimen for prophylaxis against pulmonary aspiration in the patient with a full stomach. However, its effect on IOP is not known.

In our study we have demonstrated that metoclopramide does cause some significant initial increase in IOP. The initial elevation usually returns to normal or just above normal IOP levels within 30 minutes. This increase along with the increase in IOP caused by succinylcholine, could produce serious effects on the "open" eye resulting in extrusion of the vitreous contents and possibly blindness. Several studies[2] have shown that pentothal causes a decrease in IOP on induction of anesthesia. This was confirmed in our study of the control group of patients (Group I). This depressant effect of pentothal was slightly attenuated by metoclopramide (Group II) and in some patients, there appeared to be a slight elevation of IOP. Further, the anticipated increase in IOP in patients receiving succinylcholine was augmented in patients who received metoclopramide. Consequently, although the samples were small, our study demonstrated that metoclopramide raises IOP and has a synergistic effect with succinylcholine as far as the effect on IOP is concerned. Further studies are needed before it can be concluded that metoclopramide is relatively contraindicated in patients with perforated eye injuries.

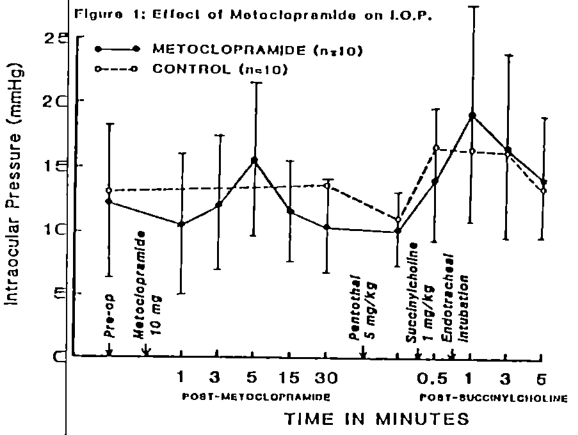
Figure 1: Effect of Metoclopramide on I.O.P.

References.

1. Albibi R, McCallum RW. Metoclopramide: pharmacology and clinical application. Annals of Int Med 98:86-95, 1983.
2. Schreuder M, Linssen GH. Intraocular pressure and anesthesia. Anaesthesia 27:165-170,1972.

Title: VALUE OF SKIN TESTS IN ANESTHETIC MANAGEMENT OF SYSTEMIC MASTOCYTOSIS

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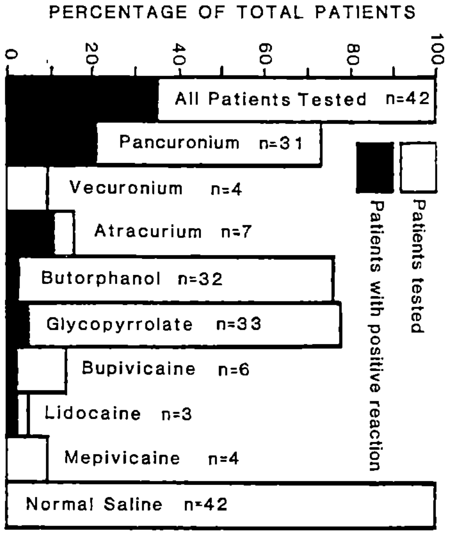
Introduction. Anesthesia in patients with systemic mastocytosis (SM) is characterized by peri-operative complications which may culminate in cardiovascular collapse and death.[1] In order to minimize these problems, intradermal skin tests were utilized for their qualitative and quantitative prognostic value. The value of this information pre-operatively is useful in planning which agents may be relatively[2] and absolutely contraindicated for a given patient. Skin tests also appear to correlate with the other biochemical indications of SM.

Methods. Forty-two patients with SM were seen at our institution for a variety of surgical procedures, ranging from renal artery bypass graft to dental extraction. Wherever possible regional anesthesia was utilized. The group to whom regional anesthesia was administered received intradermal skin tests with a local anesthetic (always an amide-linied agent) and also a muscle relaxant, an analgesic agent and an anticholinergic agent in order to have available tested agents for endotracheal intubation (if necessary), to control pain post-operatively and to treat bradycardia. The group to whom general anesthesia was administered received intradermal skin tests with the muscle relaxant, analgesic agent and an anticholinergic agent. In both groups of patients, preservative-free normal saline was used as a control for the other agents being tested. Informed consent was obtained from all the patients having the intradermal tests.

The skin tests were performed on the volar surface of the patient's forearm with 0.1 ml of the agent being tested and the area over the intradermal skin puncture was lettered and circled with a skin marking pencil. A test was interpreted as positive when the erythematous and indurated wheal developed with a diameter in excess of one (1) centimeter. Prior to the administration of the test, resuscitative equipment and drugs including epinephrine infusion were prepared and available for managing any untoward reactions resulting from the skin tests.

Results. Figure 1 shows that approximately one-third of all the patients with SM developed positive reactions after intradermal skin testing. This was not only true of the regional and general anesthesia groups, but the entire group of patients as a whole. Nine of the 15 patients who developed positive tests demonstrated elevated urinary metabolites of prostaglandin-D_2 and 6 of the 15 paients who developed complications, demonstrated positive responses to intradermal skin tests.

Discussion. Though relatively rare, SM a clinical syndrome which can produce serious morbidity and if untreated, mortality when exacerbation occurs under anesthesia. The use of intradermal skin tests appears to have significant prognostic value in identifying those patients susceptible to developing the complications of SM. A quantitative estimate of risk can also be crudely determined and this appears to correlate satisfactorily with the biochemical tests that are diagnostic of SM.



References.

1. Roberts LJ, Sweetman DJ, Lewis RA, Alston KF, Oates, JA: Increase production of prostaglandin D_2 in patients with systemic mastocytosis. N Engl J Med 1980; 303:1400.

2. Scott HW, Parris WCV, Sandidge PC, Oates JA, Roberts LJ: Hazards in operative management of patients with systemic mastocytosis. Ann Surg 1983; 197:507.

Supported by the Study Center for Anesthesia Toxicology, Vanderbilt.

Title: ANESTHESIA FOR LIVER TRANSPLANTATION WITH VENO-VENOUS BYPASS:
PHYSIOLOGIC CONSIDERATIONS

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Introduction. Patients undergoing liver transplantation provide a challenge for the anesthesiologist in terms of length of procedure, hemostasis, metabolic abnormalities and hemodynamic instability. Measurements were made to illustrate the multiple physiologic changes encountered.

Methods. A retrospective analysis of data acquired from 28 consecutive patientswith end stage liver disease included arterial, pulmonary artery, and central venous pressures; continuous core temperature; thermodilution cardiac outputs; O_2 consumption and CO_2 production from the mass spectrometer; arterial blood gases, colloid oncotic pressure, serum osmolarity and electrolytes (Na+, K+, Ca++ and glucose). Systemic and pulmonary vascular resistances were computed. Urine output was recorded every half hour. Coagulation studies and the thrombelastograph (TEG) were used to monitor hemostasis.

Results. The data that follows were obtained from measurements relatively free of pharmacologic influence and are expressed as mean changes ± 1 S.D. Preanhepatic hemodynamics revealed an elevated cardiac index (4.4L/M2 ± 1.2, n=28), a decreased SVR (752.1 dyne sec/cm5 ± 290.5, n=28) and a decreased PVR (93.6 dyne sec/cm5 ± 27.3, n=26). The anhepatic phase was associated with transient decreases in core temperature (3.7<C ± 1.1, n=16) and heart rate (16.7% ± 5.6, n=16) upon initiation of veno-venous bypass with room temperature prime. Oxygen consumption decreased (23.7% ± 6.2, n=18) following removal of the recipient organ from the circulation. Measurements made during the late anhepatic phase showed a decrease in CO (38.3% ± 12.8, n=22) and concomitant increases in SVR (71.6% ± 49.6, n=22) and PVR (44.0% ±19.8, n=21). Urine output fell (84.5ml/hr ± 109.2, n=15) during the anhepatic phase. Following cold saline flush of the donor organ, reestablishment of blood flow resulted in transient decreases in temperature (2.0<C ± 1.0, n=16), heart rate (20.1% ± 12.4, n=11) and mean arterial pressure (23.2% ± 11.0, n=11). Cardiac outputs, obtained as soon as a stable baseline permitted following reperfusion of the donor organ (within 2 minutes), were consistently increased (92.0% ± 40.1, n=11), while decreases were calculated in SVR (54.6% ± 13.6, n=11) and PVR (43.0% ± 16.3, n=11). Ten minutes following unclamping, whole blood determinations increased for K+ (0.85 mEq/L ± 0.5, n=22), $PaCO_2$ (6.5 mmHg ± 3.9, n=22), base deficit (3.2mEq/L ± 2.4, n=22) and glucose (152.2ng/dl ± 62.5, n=21), while pH decreased (0.09 ± 0.05), n=22). PaO_2, Na+ and ionized calcium showed no significant changes. Colloid oncotic pressure decreased (1.93mmHg ± 1.5, n=21) as did hemoglobin (0.77mg/dl ± 0.62, n=21, while serum osmolarity increased (8.71mOsm ± 12.0, n=21). Urine output fell further during the first half hour following unclamping (37.3ml/hr ± 34.5, n=15), but increased during the second half hour (46.7ml/hr ± 47.5, n=15) and usually increased further thereafter. TEGs obtained post unclamping demonstrated prolonged reaction time, decreased maximum amplitude and decreased clot growth angle. Mean [illegible] pressure increased (41.5% ± 17.8, n=11), reaching a peak after approximately 15 minutes. During the postanhepatic phase, oxygen consumption and CO_2 production were increased to control levels or above. Core temperature decreased during the preanhepatic phase (0.27<C/hr ± 0.18, n=16), with a step decrease (0.46<C ± 0.14, n=16) at the start of bypass and a further decrease (0.85<C/hr ± 0.33, n=16) during bypass. Reperfusion of the donor organ resulted in another step decrease (0.59<C ± 0.24, n=16) in core temperature followed by gradual rewarming (0.38<C/hr ± 0.15, n=16) for the remainder of the procedure. Three patients exhibited profound bradycardia and hypotension which required aggressive therapy following re-establishment of blood flow to the donor organ. These data were consistent but extreme and therefore not included above.

Discussion. The elevated preanhepatic cardiac index and lowered vascular resistance has been suggested to result from peripheral A-V shunts associated with liver disease. During the anhepatic phase the venous return is decreased even with veno-venous bypass, resulting in a decreased cardiac output and a compensatory increase in SVR. Decrease in heart rate associated with restablishment of blood flow to the donor organ can be attributed in part to the effect of rapid temperature change upon the sinoatrial node as the cold hepatic effluent enters the circulation. However, comparison of the temperature change upon initiation of veno-venous bypass with the temperature change at revascularization, suggests that potassium and possibly other substances released from the hepatic effluent potentiate the slowing of heart rate, occasionally causing profound bradycardia and hypotension. The three patients who exhibited profound bradycardia and hypotension were affected by a combination of high hepatic blood flow (as determined from pulmonary artery temperature curves) and elevated potassium from a cold liver which probably created a bolus effect of cardioplegia-like solution. As indicated by the changes in colloid oncotic pressure and serum osmolarity, the hepatic effluent created a hypertonic hemodilution following unclamping. The marked fall in SVR resulted from opening the new hepatic circulation and possibly hyperkalemia in conjunction with other vasoactive substances. The elevated PA pressures may have resulted from increased cardiac output as the PVR was gradually increased due to the dissipation of the vasodilatory effect. The near doubling of cardiac output, which is at variance with Martin et al.[1], but showing similar trends to the data of Carmichael et al.[2] (without veno-venous bypass), can be explained by an increased preload and reflex mechanisms.

References:

1. Martin DJ et al. Anes Analg 63:246A, 1984.
2. Carmichael FJ et al. Anes Analg 64:108-16, 1985.

TITLE: A COST/BENEFIT ANALYSIS OF RANDOMIZED INVASIVE MONITORING IN CARDIAC SURGERY

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Introduction. Whether or not use of pulmonary artery (PA) catheters actually results in decreased morbidity/mortality, in any group of patients is controversial, as are their "cost/benefit" ratios. The addition of fiberoptic infrared mixed venous O_2 saturation (SvO_2) monitoring to PA catheters has been contended to reduce the need for routine measurements of cardiac output and blood gases if SvO_2 remains unchanged, thus reducing cost.[1] We studied the following questions in adults undergoing cardiac surgery: a) does a PA catheter of any type result in lowered mortality, morbidity, or cost compared to use of a CVP? b) does SvO_2 monitoring reduce morbidity, mortality, or cost below that incurred with use of a standard PA catheter?

Methods. This study was approved by our Human Studies Review Committee. One hundred fifty adults undergoing cardiac surgery were prospectively randomized to receive either a central venous catheter (Group I), pulmonary artery catheter (Group II), or a fiberoptic SvO_2 measuring pulmonary artery catheter (Group III). As a specific part of the protocol, if, in the medical judgment of the attending physicians, a patient first randomized to Group I should receive a PA catheter; that patient was then re-randomized to either Group II or Group III. All patients had left atrial catheters inserted intraoperatively. All patients had the following data collected during their SICU stay: numbers of cardiac outputs, arterial blood gases, hemoglobin/hematocrit determinations, total SICU stay, and hours of vasopressor and vasodilator therapy. Costs to patients of all determinations were tabulated. Prior to the study nursing and housestaff received specific training in SvO_2 monitoring, but were unaware that the nature and purpose of the study was a cost/benefit analysis. Data was analyzed with ANOVA and appropriate additional tests. $P<.05$ was considered significant.

Results. Demographic data are presented in Table 1. Of the 64 patients initially randomized to Group I (CVP), 40 were re-randomized between Groups II (n=26) and III (n=14). The patients who remained in Group I had a higher percentage of CABG performed. Between Groups II and III there were no significant differences in indices of severity of illness or types of surgery. Table 2 presents ICU stay and vasoactive drug requirements, and Table 3 presents total costs for lab, hemodynamic determination, and the catheters themselves. Total average costs were: Group I \$551.53±14.77; Group II \$930.55±47; Group III \$1,277.57±151, each significantly different. Cardiac outputs were not possible in Group I, but there were actually more cardiac outputs performed in Group III (n=5.75), than in Group II (n=3.07) despite the SvO_2 monitoring. Arterial blood gas costs were: Group I \$193.38±23.04, Group II \$258.61±20.26, and Group III \$294.82±53.27 (NS). There was no detectable catheter-related morbidity in any patient. SICU stay was 1.35±.73, 1.87±.22, 3.18±.87 in Groups I, II, and III, respectively (NS). No other specific morbidity differences between groups were found. Deaths were 0, 1, 1 in Groups I, II, III, respectively (NS).

Discussion. The fact that 40 patients initially randomized to the CVP group were re-randomized between the two PA groups, at attending physician medical discretion, indicates that severity of illness was less in Group I (and greater in Groups II, III). Group I patients incurred almost half the cost with no added morbidity or mortality. Severity of illness was probably equal between Groups II and III. The hypothesis that SvO_2 monitoring might eliminate need (and cost) for some ABG's and CO's was not found true in our study. Indeed, we found no morbidity or mortality related rationale for justifying the 27% extra average cost of SvO_2 monitoring.

Conclusion. a) Patients who have good cardiac function could safely undergo cardiac surgery with CVP monitoring at less cost; b) patients who appear to require PA catheter monitoring were not benefited in mortality, morbidity, or cost by addition of SvO_2 monitoring.

Reference. 1. Norfleet EA, Watson CB, "Continuous mixed venous oxygen saturation measurement: A significant advance in hemodynamic monitoring?" J. Clin. Monitoring 1:245-258, 1985.

Table 1. Patient characteristics.

Group	Number of Patients	CABG	Valve	CABG+Valve
I	24	22 (91.7%)	0	2 (8.3%)
II	77	52 (67.5%)	15 (19.5%)	10 (13%)
III	47	33 (70.2%)	7 (14.9%)	7 (14.9%)
P		<0.05	NS	NS

Table 2. Length of stay and vasoactive drug requirements (Mean ± S.E.M.).

Group	Stay (Days)	Dilators (Hours)	Pressors (Hours)
I	1.35±0.73	6.29±1.15	1.63±0.99
II	1.87±0.23	15.41±4.12	14.43±1.62
III	3.18±0.87	19.71±6.63	13.65±6.00
P	NS	NS	NS

Table 3. Mean costs (Mean ± S.E.M.).

Group	ABG Costs	C.O. Costs	Total Costs	Hb/HCT
I	\$193.38±23.04	------	\$ 551.53±14.77	\$25.67±3.1
II	\$258.61±20.26	\$230.39± 31.19	\$ 930.55±47.38	\$32.32±1.92
III	\$294.82±53.27	\$430.71±121.51	\$1,277.27±151.35	\$41.29±6.8
P	NS	0.05	0.02	NS

Title: NONINVASIVE MONITORING OF CARBON DIOXIDE: TRANSCUTANEOUS VERSUS END-TIDAL PCO2

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Introduction. Arterial blood gas (ABG) analysis for carbon dioxide partial pressure (PaCO2) is the traditional method of documenting the adequacy of ventilation in the operating room. Disadvantages of ABG sampling include its intermittent nature, high cost, and the risk of complications. End-tidal PCO2 (PetCO2) and transcutaneous PCO2 (PtcCO2) have been shown to correlate with PaCO2. Both PetCO2 and PtcCO2 values can be obtained non-invasively and continuously, and hence are attractive alternatives to ABG analysis. The purpose of this study is to compare PetCO2 and PtcCO2 as monitors of PaCO2 in the anesthetic management of adult patients.

Materials and Methods. This study was conducted on adult patients under general anesthesia for surgery. Human Subjects Review Board approval was obtained for the study. PetCO2 values were obtained with a Hewlett Packard model 47210A capnometer. PtcCO2 values were measured by a Novametrix Model 850 monitor. The sensor was heated to 44°C and calibrated with a two point dry gas calibration method, using 5 and 10 percent CO2 as recommended by Monaco et al.(1). The sensor was allowed to warm up on the skin for ten minutes before data were collected. The arterial blood samples were analyzed for blood gases with an Instrumentation Laboratories IL813. The PaCO2 values were not corrected for patient temperature. PaCO2 values were plotted versus both PtcCO2 and PetCO2. The data were analyzed by linear regression and calculation of the correlation coefficient (r). The accuracy of prediction of PaCO2 was assessed by calculating the standard error of the estimate (SEE), and the 95% confidence limits. The mean and standard deviation of the differences (PaCO2 - PtcCO2 and PaCO2 - PetCO2) were also calculated. The mean of the differences is a measure of the bias and the standard deviation of the differences is a measure of the precision.

Results. 246 data sets were collected from 24 patients, 9.8 ± 3.6 (mean ± SD) data sets per patient. 208 of these sets included PetCO2 values. The 38 sets without PetCO2 values were collected either before endotracheal intubation or after extubation. The mean ± SD of data collected are: patient's age = 46 ± 17 years, patient's weight = 77 ± 27 kg, PaCO2 = 39.1 ± 8.7 mmHg, PtcCO2 = 37.5 ± 7.7 mmHg, PetCO2 = 30.0 ± 6.6 mmHg, MAP = 82 ± 17 mmHg, H.R. = 89 ± 22 beats/min, temp. = 35.5 ± 1.3° C, R.R. = 12 ± 5 breaths/min. Linear regression analysis produced the following: PaCO2 = 0.86 PetCO2 + 12.2, r = 0.68 (P < 0.001), SEE = 6.2; PaCO2 = 1.00 PtcCO2 + 1.78, r = 0.87 (P < 0.001), SEE = 4.3. The bias and precision for the PaCO2 - PetCO2 difference are 8.0 and 6.2 mmHg; for the PaCO2 - PtcCO2 difference, they are 1.6 and 4.3 mmHg.

Discussion. PetCO2 monitoring is valuable because it reflects instantaneously the mixed alveolar PCO2 from each breath. PetCO2 is sensitive to changes in physiologic dead space and therefore is helpful in detecting esophageal intubation and pulmonary embolism. However, this sensitivity to dead space also implies that the PaCO2 - PetCO2 difference may change during anesthesia. PetCO2 monitoring is also limited to some extent by the practical necessity of intubation. Unlike PetCO2, PtcCO2 can be followed prior to and after intubation. Disadvantages of PtcCO2 monitoring include the necessity of calibration, a 5 min. warm-up period on the patient, and the possibility of causing 1st degree skin burn. No patients received burns in this study. Our data show that both PtcCO2 and PetCO2 are closely correlated to PaCO2. The larger bias for PaCO2 - PetCO2 compared to PaCO2 - PtcCO2 is a result of physiologic dead space, and therefore does not mean that PetCO2 correlates less with PaCO2. However, the larger precision for PaCO2 versus PetCO2 does indicate that PtcCO2 follows PaCO2 more closely than does PetCO2. Finally, PtcCO2 has a smaller 95% confidence interval for predicting PaCO2, and a linear regression line which approximates more closely the line of identity.

References.

1. Monaco F, McQuitty JC, and Nickerson BG. Calibration of a heated transcutaneous carbon dioxide electrode to reflect arterial carbon dioxide. Am Rev Respir Dis 127:322-324, 1983

Figure 1

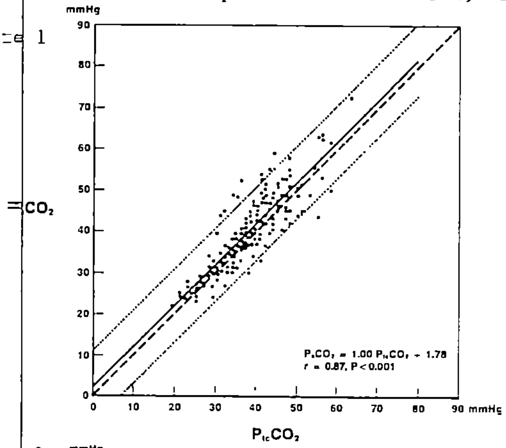
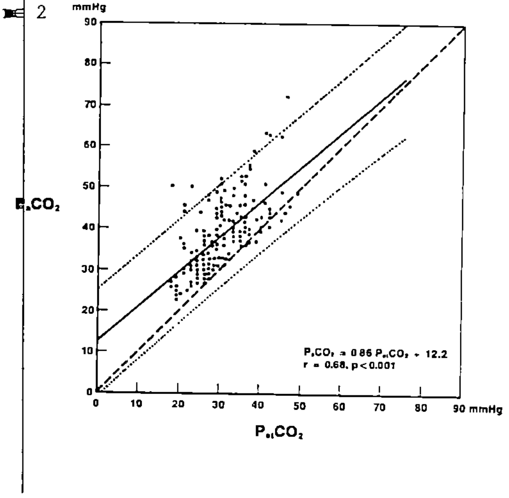


Figure 2



Title: EPIDURAL SUFENTANIL IN LABOR

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Introduction. The use of epidural narcotics in labor has been disappointing because of failure to adequately relieve pain. However, fentanyl and bupivicaine combined are more effective than either drug along in providing analgesia in labor (1). Sufentanil which has a higher affinity for the opiate receptor than does fentanyl may be the opioid of choice for epidural analgesia as it has a longer duration of action (2,3). A double blind study was done to examine the analgesic effect of three differences doses of sufentanil added to epidural bupivicaine.

Methods. Approval by the Institutional Review Board for Human Investigation, and informed consent from the patients were obtained. Forty women in labor (34 primips, 6 multips) with uncomplicated pregnancies, and a singleton fetus were studied. All patients had a lumbar epidural catheter placed at L 2-3 or L 3-4 interspaces, and received a test dose of 3 ml's of 1.5% lidocaine thru the catheter. This was followed by 7 ml's of 0.25% bupivicaine, and 1 ml of solution from a coded ampule. The content of the ampule was as follows: Group 1, saline; Group 2, 10 µg of sufentanil; Group 3, 20 µg of sufentanil; Group 4, 30 µg of sufentanil. All subsequent dosing of the patients was with 0.25% bupivicaine. Visual analog pain intensity scores were recorded prior to epidural placement and at 10 and 30 minutes post-epidural injection. Time to first painless contraction (onset time) and time to epidural top-up (duration) were recorded. Apgar scores were assessed at 1 and 5 minutes post-delivery. Comparison was made between the 4 groups by analysis of variance.

Results. Patients in the four groups were comparable in age, parity, height, weight and baseline pain intensity scores. At 10 minutes pain relief was significantly greater in Group 4 ($P<0.01$), than in the control group (see Table 1). By 30 minutes all patients had adequate analgesia and there was no difference in pain scores between the groups. Time to first painfree contraction (onset time) was not significantly different between the groups. There was a dose-related increase in duration of analgesia compared to control, which just failed to achieve significance for Group 2 ($0.1>P>0.05$), but was significant for Groups 3 and 4 ($P<0.01$). Side effects were minimal. One patient in Group 1 had a short period of hypotension which responded to fluid therapy. One patient in Group 2 and one in Group 4 complained of transient pruritis, which did not require treatment. Fetal outcomes were uniformly good. There was no significant difference in Apgar scores between the four groups at either 1 or 5 minutes.

Discussion. This study clearly demonstrates that combining sufentanil with bupivicaine provides more prolonged analgesia than does bupivicaine alone when administered epidurally for analgesia during labor. This benefit is achieved with little cost in terms of additional side effects. 20 µg apparently is the optimum dosage of sufentanil as no significant increase in duration results when the dose is increased to 30 µg. There is, however, more rapid onset of analgesia at the higher dose which may be desirable in certain cases. Advantages of the combination include less frequent top-ups; reduction in total dose of local anesthetic; less risk of hypotension and minimal motor blockade.

References.

1. Youngstrom P, Eastwood D, Patel H, Bhatia R, Cowan R, Sutheimer C. Epidural fentanyl and bupivicaine in labor: double blind study. Anesthesiology 1984; 61:A414.
2. Leysen JE, Gommeren W, Niemegeers CJE. [^{3}H] sufentanil, a superior ligand for µ opiate receptors: binding properties and regional distribution in rat brain and spinal cord. Eur J Pharmacol 1983; 87:209-25.
3. Donadoni R, Rolly G, Noorduin H, Vandenbusche G. Epidural sufentanil for postoperative pain relief. Anaesthesia 1985;40:634-38.

TABLE 1.	GROUP 1	GROUP 2	GROUP 3	GROUP 4
		10 µgs	20 µgs	30 µgs
	Saline	Sufentanil	Sufentanil	Sufentanil
Initial pain score[a]	76 (17.4)	69 (16.7)	82 (9.0)	77 (11.7)
% reduction[a] at 10 minutes	58 (18.5)	78 (22)	74 (29.4)	90 (16.6)*
% reduction[a] at 30 minutes	96 (8.3)	97 (7.1)	95 (10.2)	98 (5.4)
Analgesia onset[a] in minutes	16 (5.2)	13.6 (8.5)	15.5 (8.9)	9.7 (5.3)
Analgesia duration[a] in minutes	90 (19.6)	114 (17.3)	137 (28.9)*	144 (35.3)*

[a], All figures expressed as mean S.D. in parenthesis

* $P < 0.01$

Title: REVERSAL OF THE ADVERSE CARDIOVASCULAR EFFECTS OF INTRAVENOUS DILTIAZEM IN ANESTHETIZED DOGS

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Introduction Intravenous Diltiazem (D) is now available and is used for the treatment of myocardial ischemia, supraventricular dysrhythmias and hypertension. Significant adverse effects including A-V block and hypotension of prolonged duration have been reported following intravenous use of D (1,2). The risk of developing these adverse effects is further increased during general anesthesia due to depression of the compensatory sympathetic outflow and potentiation of these effects by the volatile agents. At the present time there is controversy over which drug is more effective in reversing these sequelae (3). This investigation was designed to study reversal of the hemodynamic effects of D with $CaCl_2$ (Ca) and epinephrine (epi).

Methods Eight mongrel dogs were anesthetized with thiamylal sodium (5-7 mg/lb) IV, intubated and ventilated to normocapnea with a mixture of 70% N_2O and 30% O_2. Fentanyl (300 mcg/kg) was given as an IV bolus followed by an infusion at 1.5 mcg/kg/min. Monitoring was continuous with direct arterial, pulmonary arterial and Millar LVdp/dt catheter pressure recordings, and ECG. Intermittant measurements were recorded of PCWP, CO, and ECG at 50 mm/sec. Following control measurements, D was administered IV as a bolus injecton of 300 mcg/kg. After each infusion period, the D infusion was increased by 30 mcg/kg/min preceded by another bolus until significant hemodynamic or electrophysiologic changes occurred. Criteria of a significant change included a 50% decrease in MAP along with a) significant A-V block (2°or3°); b) a 50% decrease in CI; or c) a 50% decrease in dp/dt. When one of these events occurred the infusion of D was discontinued. If there was no improvement after 5 minutes, Ca (40 mg/kg) IV was given followed 2 to 3 minutes later by a second bolus of Ca. If there were still no improvement 5 minutes after the second bolus of Ca, epi was injected (1 mcg/kg) followed 1 minute later by 2 mcg/kg if there were no response to the initial bolus. A maintenance infusion of epi was then started at 8-12 mcg/min for a period of 30 minutes. Short periods of atrial and ventricular pacing were performed during the control, D, and treatment periods. Multiple blood samples were obtained during the study to determine electrolyte levels as well as blood gas tensions. Blood for serum D levels was obtained at the onset of the first significant side effect (D_1) and at the end of the D infusion (D_2).

Results The mean serum [D] for D_1 was 423±72 and for D_2 was 1941±56 ng/ml. The mean hemodynamic variables are shown in Table I. D produced significant reductions of SVRI, MAP, SBP, and DBP. LVdp/dt was not significantly depressed; RA, PCWP, and CI were not significantly affected. D produced a high incidence of A-V conduction disturbances (Table II) ranging from 1° to 3° blocks. The administration of Ca had no significant effect on any of the hemodynamic variables. In fact, Ca decreased HR and produced sinus arrest with a ventricular escape rate of only 20 BPM in two dogs. Epi significantly increased HR, MAP, SBP, and DBP. It decreased 2° and 3° block to 1° block and partially reversed 1° block by decreasing the P-R interval as measured by ECG. Atrial and ventricular pacing did not significantly improve any of the adverse effects.

Discussion This study confirms that D infusion in higher concentrations predominantly produces A-V conduction depression and profound hypotension. Epi infusion proved to be most effective in attenuating and eliminating each of these side effects. In contrast, Ca did not significantly increase heart rate or blood pressure, or reverse A-V block. In 2 instances Ca produced further depression of the A-V conduction, bradycardia and sinus arrest. Although Ca slightly increased LVdp/dt and CI, MAP was not affected and SVRI was further decreased, indicating that Ca should be used with caution and only after the calcium channels have been reopened by epi.

References

1. Kapur PA, Tippit SE: Correlation of cardiovascular effects with plasma levels of diltiazem during isoflurane anesthesia. Anesthesiology 1984; 61:A12.
2. Mazzon P, Giffin J, Cottrell J et al: Intracranial pressure during diltiazem-induced hypotension in anesthetized dogs. Anesth Analg 1985; 64:1001-1004.
3. Haiman RJ, Maniardi LH, McAllister J: Reversal of the cardiovascular effects of verapamil by calcium and sodium. Circulation 1979; 59:787-809.

TABLE I

	CONTROL	D_1	D_2	CaCl	Epi
HR (bpm)	92±38	77±16	66±16	55±21	96±27*
MAP (mmHg)	93±17	62±21	48±10#	47±11	72±8*@
SVRI (dyne sec/cm^5/m^2)	2287±888	1265±390	1007±376#	842±243	1034±319

Values = Mean±SD; $p<0.05$ for * between epi and Ca; # between control and D_2; @ between D_2 and epi

TABLE II

NUMBER OF NEW CONDUCTION DISTURBANCES APPEARING DURING INFUSION OF DILTIAZEM

	D_1	D_2	Total
1 degree block	7	1	8
2 degree block type I	1	2	3
2 degree block type II	1	3	4
2 degree block type II with aberrant conduction	–	1	1
3 degree block	–	1	1
A-V junctional rhythm	2	1	3
TOTAL	11	9	20

Title: THE HEMODYNAMIC EFFECTS OF PROPOFOL AND THIAMYLAL SODIUM FOR INDUCTION IN CORONARY ARTERY SURGERY

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Introduction As the search for new intravenous induction agents continues, propofol (ICI 35,868) appears to show some promise. Studies in healthy patients undergoing various surgical procedures have demonstrated smooth inductions with rapid recovery and few excitatory side effects. However, drugs suitable for use in healthy patients frequently have different effects in patients with cardiac disease or other debilitating conditions. This study was designed to 1) compare propofol (P) with thiamylal sodium (T) with regard to their safety and efficacy for induction, and 2) to compare the hemodynamic effects of these two drugs using invasive cardiac monitoring in patients with coronary artery disease undergoing coronary artery bypass surgery (CABG).

Methods After obtaining IRB approval and informed written consent, 16 patients aged 30-75 years and ASA class IV undergoing elective CABG were studied. All patients had ejection fractions 30% and no history of myocardial infarction within 3 months. Patients were maintained on their usual regimen of cardiac drugs, including beta and calcium channel blockers and nitrates, until the morning of surgery. Premedication was morphine, 0.1 mg/kg, and scopolamine, 0.4 mg, administered IM, 1-1½ hours prior to induction. Monitors included ECG lead V_5 and radial and pulmonary arterial catheters. Systemic and pulmonary arterial pressures, systemic vascular resistance (SVR), cardiac index (CI), heart rate (HR), stroke index (SI), and left ventricular stroke work index (LVSWI) were recorded at 1 (T_1) and 3 (T_3) minutes after drug administration and before intubation (T_4). Patients were randomly assigned to receive either propofol, 2.5 mg/kg, or thiamylal, 4.0 mg/kg, IV, for induction with the full dose being administered over 30 seconds. At the end of 3 minutes, patients were given pancuronium, 0.1 mg/kg, IV, and halothane, 0.25-2%, and intubated when suitably anesthetized. Results were analyzed using an analysis of variance of repeated measures with a significance of $p < 0.05$.

Results Between control values and T_3, propofol caused a significant decrease in MAP, SVR, and LVSWI, and a significant increase in HR while no change was seen in PCWP or CI. Thiamylal produced no significant hemodynamic changes during this same period. Significant differences between groups were seen in MAP and SVR at T_3 (Table). Addition of halothane (T_4) to propofol resulted in significant decreases in MAP, SVR, PCWP, and LVSWI, and an increase in HR. The thiamylal group showed significant decreases only in MAP and LVSWI at T_4, and differences between groups were limited to SVR. No significant complications were seen during the induction period with the use of either drug.

Discussion Propofol, a new intravenous induction agent, has been shown to be safe and effective in animals and man, both for the induction of anesthesia and when used in incremental doses for short procedures (1). It has a rapid distribution phase (t ½ α ~ 2.5 minutes) and a slower elimination phase (t ½ β ~ 55 minutes) and is metabolized and excreted, primarily through urine. Though originally in Cremophor CL formulation, it is now available in an aqueous emulsion which was used in this study (2). Previous studies have shown significant decreases in MAP and SVR in both healthy patients (3) and those with documented coronary artery disease (4). The effects have mainly been attributed to the vasodilatory effects of propofol. The fact that our study shows no change in PCWP or CI, and a decrease in LVSWI, indicates that the effects of propofol are probably due to both vasodilatation and myocardial depression. However, the effects are transient and resulted in no adverse sequelae. Therefore, we suggest that propofol and thiamylal are both safe and effective for use in the induction of patients with coronary artery disease.

References

1. Glen JB: Animal studies on the anaesthetic activity of IC 35,868. Brit J Anaesth 1980; 52:731.
2. Glen JB, Hunter SC: Pharmacology of an emulsion formulation of ICI 35,868. Brit J Anaesth 1984; 56:617.
3. Grounds RM, Morgan M, Lumley J: Some studies on the properties of the intravenous anaesthetic, propofol (Diprivan) - a review. Postgraduate Medical J 1985; 61(Suppl 3):90-95.
4. Patrick MR, Blair IJ, Feneck RO, Sebel PS: A comparision of the haemodynamic effects of propofol (Diprivan) and thiopentone in patients with coronary artery disease. Postgraduate Medical Journal 1985; 61(Suppl 3):23-27.

		CONTROL	T_1	T_3	T_4
MAP	(P)	97±1[illegible]	83±18#	75±16^{+}*	66±9*
	(T)	95±13	93±10	95±8	77±11*
HR	(P)	60±14	72±19*	68±12#	71±10*
	(T)	67±12	75±11#	67±8	71±8
CI	(P)	2.4±0.4	2.4±0.4	2.4±0.5	2.6±0.6
	(T)	2.8±1	2.8±0.8	2.5±0.6	2.4±0.9
PCWP	(P)	16±5	15±5	14±5	12±4#
	(T)	18±3	18±3	17±3	15±4
SVR	(P)	1565±262	1246±328#	1146±227^{+}*	987±291^{+}*
	(T)	1426±450	1379±442	1522±349	1307±358
LVSWI	(P)	45±10	28±9*	30±10*	28±8*
	(T)	44±15	37±10	39±9	29±14

+ $p < 0.01$ between groups # $p < 0.05$ within groups
* $p < 0.01$ within groups $\bar{x}$ ± 1 SD

Title: IMPROVED POSTOPERATIVE ANALGESIA: EPIDURAL VS PATIENT CONTROLLED INTRAVENOUS MORPHINE

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Introduction. Epidural Morphine (EM) and Patient Controlled Analgesia Morphine (PCAM) administration are both becoming popular methods of providing improved postoperative analgesia^{1,2}. To our knowledge, no controlled prospective studies have compared these approaches in patients following surgery. The objective of this study was to compare and contrast EM and PCAM with a standard Intramuscular Morphine (IMM) regimen, in patients undergoing total abdominal hysterectomy (TAH) to determine if one or more of the techniques allowed patients to mobilize, eat or be discharged from the hospital sooner because of improved pain relief. In addition, comparison was made of the analgesic effectiveness of each approach, as determined by patient and investigator.

Methods. With approval by our human institutional review board and informed consent, we randomized 46 ASA I and II patients undergoing TAH to three groups. Group I received IMM 0.10-0.15 mg/kg 2-3 hourly as required, commencing on arrival in the recovery room. Group II received PCAM commencing with 0.5 mg increments until comfortable in the recovery room, and subsequent 0.5 mg doses with a programmed lock-out period of 6 mins. Group III received EM 5 mg in 10 cc saline at completion of surgery and 2.5 mg in 5 cc saline repeated as required. All patients received identical anesthetic techniques of precurarisation with 3 mg dtc, sodium thiopenthal 3-5 mg/kg vecuronium 0.1 mg/kg and maintenance with 1% isoflurane and 70% nitrous oxide in oxygen. Intraoperative analgesia was provided with fentanyl 0.1-0.3 μgm/kg given shortly after induction. Epidural catheters were placed at L3/L4 following induction but prior to incision, placement being confirmed by loss of resistance to air. The Abbott PCA device was attached to a peripheral IV infusion on arrival in the recovery room. The following criteria were assessed every 4 hrs for 36 hrs following initial morphine dose: patient subjective pain score by 10 cm visual analog scale; objective pain on a 1-3 scale (moaning, crying, and diaphoresis 3; movement of patient limited by pain 2; patient moving freely with some discomfort on coughing 1); objective sedation on a 1-3 scale (sleeping most of the time 3; usually asleep but awakening to outside stimuli 2; awake watching television or reading 1). The following milestones were looked for every 4 hrs and the times they were achieved were charted: first time to mobilization (sit on edge of bed, sit in chair, walk 5 paces unaided); first solid food meal following return of bowel sounds; time to readiness for discharge (criteria being patient afebrile $< 99^{\circ}$F, able to walk 20 steps unaided, able to eat solid food); and, patient acceptability, on a 10 cm visual analog scale. All observations were made by an impartial observer, unaware of the analgesic regimen. Statistical analysis was by Wilcoxon rank sum test, analysis of variance and student t-test.

Results. 15 patients received EM, 18 IMM and 13 PCAM. Mean subjective pain scores were significantly better during the first 36 hours in the EM group 3.35 ± 2.97 compared to IMM 4.11 ± 2.89 and PCAM 4.06 ± 2.77, ($p < 0.05$). In addition, there was a significantly higher frequency of low (≤ 3) subjective pain scores, 80/140 in the EM group compared to IMM 48/116 and PCAM 67/107 ($p < 0.05$) There was no significant difference in subjective or objective pain scores between IMM and PCAM. Despite receiving better analgesia, those patients receiving EM did not mobilize, begin to eat or attain discharge criteria any sooner than IMM or PCAM. Itching, requiring treatment, occurred in 1 EM patient, and 2 IMM patients one of whom had to be withdrawn from the study. Nausea and vomiting occurred with similar frequency in all groups. No patient experienced clinical evidence of early or late respiratory depression.

Conclusion. The results of this study demonstrate that while epidural morphine provides more effective analgesia, following TAH, than IM or PCA morphine, patients are not able to mobilize, eat or fulfill discharge criteria sooner. Nevertheless, patient acceptability and enthusiasm for epidural and PCA analgesia should prompt further studies, perhaps with continuous infusion of epidural narcotics, in the hope of shortening hospital stay with improved analgesia.

References

1. Graves DA, Foster TS, Batenhorst RL, Bennett RI and Baumann TJ: Patient controlled analgesia. Ann Int. Med. 99:360-366, 1983

2. Cousins MJ and Mather LE: Intrathecal and epidural administration of opioids. Anesthesiology 61:276-310, 1984

Title: PLASMA BETA-ENDORPHIN LEVELS IN TERM AND PRETERM NEONATES

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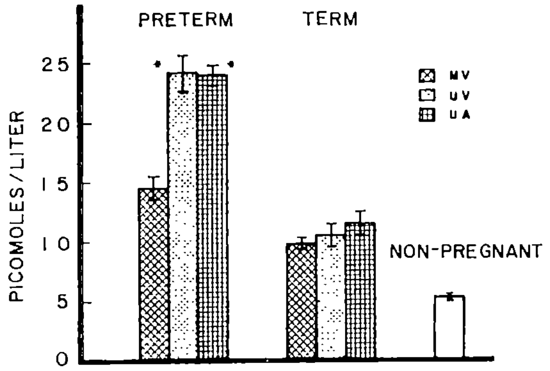
Introduction. Plasma beta-endorphin (B-END) levels are increased during gestation and in full term neonates. Although the function of circulating B-END in pregnancy is still undefined, it has been postulated to produce: 1) changes in mood and smooth muscle tone in the mother; 2) inhibition of fetal breathing and 3) modulation of responses to hypoxia during delivery. Points 2 & 3 are supported by the known inhibitory effects of B-END on respiratory function. Althogh B-END plasma levels have not been determined in preterm neonates, naloxone (an opioid antagonist) has been shown to reverse apnea in preterm neonates. The present study shows significantly elevated B-END plasma levels in venous and arterial cord blood in preterm when compared to term neonates.

Methods. The research protocol was approved by the Institutional Board of Research Associates for application to human subjects and all patients gave informed consent. Sixteen patients undergoing cesarean section (CS) were studied: 8 required preterm CS at $<$ 35 weeks gestation for premature rupture of membranes (3 received ritodrine for tocolysis and 5 dexamethasone for surfactant maturation) and 8 were scheduled for elective CS at term. All patients received lumbar epidural anesthesia induced by 1.5% lidocaine with epinephrine 1:200,000 in 5 ml increments in order to acheive a T_6 sensory level. At the time of delivery, maternal venous (MV), neonatal umbilical venus (UV) and arterial (UA) blood samples were collected for B-END determination. Maternal arterial and UV and UA blood pH and gas tensions were also measured. Neonates weight and Apgar scores were noted. Blood samples were also collected from 8 non-pregnant females prior to anesthesia induction for non-obstetric surgery, to serve as a control group. Plasma B-END was measured by radio-immuno assay (Immunonuclear Inc., Stillwater, MN 55082). Results are expressed as mean ± 1 SE and differences among groups analyzed using the student's t-test.

Results. Birth weight was 3640 ± 150 g for term neonates and 1956 ± 170 for prematures. All term neonates had Apgar scores of $>$ 7 at one minute and $>$ 9 at 5 minutes, while two preterm neonates had scores of 4 and 7 at 1 and 5 minutes respectively. All term neonates had an uneventful nursery course but three preterm developed respiratory distress. Maternal, UV and UA blood pH and gas tensions were similar in term and preterm patients (data not shown). The figure demonstrates that B-END levels were significantly higher in preterm when compared to term neonates ($P < 0.01$). It also shows that maternal plasma B-END levels were elevated when compared to non-pregnant patients; however, B-END maternal levels in preterm and term groups were not statistically different.

Discussion. Our data shows that plasma B-END levels in preterm neonates are approximately double those of term neonates. The increased B-END levels do not appear to be related to acid-base derangement. Since both UA and UV plasma B-END levels are simmilarly elevated in preterm neonates, an increased placental production of B-END could be postulated. The increased B-END levels may have among others, a depressant effect on the fetal breathing movements and could explain the higher incidence of apneic episodes, as well as their reversal by naloxone, in premature infants. It is not known at present if maternal administration of ritordine or steroids has an effect on neonatal B-END levels. Our data also demonstrates an increase in plasma B-END levels in pregnant patients, when compared to no pregnant females, supporting previous findings by other investigators.



Legend. Beta-endorphin levels in maternal (MV), umbilical arterial (UA) and venous (UV) plasma in preterm and term patients. Results are expressed as mean values; vertical bars indicate SEM.
*Statistically different from term values ($P < 0.01$)

Title: FETAL ELECTROCARDIOGRAPHIC CHANGES FOLLOWING LUMBAR EPIDURAL ANALGESIA IN LABOR

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Introduction. Local anesthetics injected into the epidural space to provide analgesia for labor and delivery have been implicated in the genesis of changes in the fetal heart rate (1). Studies to date have only examined the changes in the fetal heart rate. Examination of the waveform configuration and time intervals of fetal electrocardiogram (FECG) after the epidural administration of local anesthetics has been handicapped by the lack of a suitable technique to reliably isolate the FECG in a pure form. Using an on-line minicomputer (DEC LSI-11/23) capable of performing continuous, real time analysis of FECG (2), we studied the changes in the waveform configuration and time intervals of the FECG following lumbar epidural analgesia (LEA) in laboring women.

Methods. Institutional approval and informed consent from 10 patients receiving LEA for pain in labor were obtained. Lateral posture was meticulously maintained. Maternal blood pressure and pulse rate were closely monitored. An epidural catheter was inserted at L_2-L_3 interspace and 8 ml of plain bupivacaine (0.5%) injected slowly to achieve adequate sensory block. The FECG signal was obtained from a commercially available scalp electrode. A time coherent enhanced averaging routine was incorporated in the minicomputer's software to attenuate the noise and enhance FECG signal (3). All processing took place on-line and the output from the minicomputer comprised of the following 8 parameters of the FECG waveform: fetal heart rate (FHR), P wave area and duration, P-R interval, QRS duration, ST segment level, T wave height and R-T interval. In addition, the relationship between P-R interval of the FECG and FHR (PR-FHR correlation) during labor was studied by the calculation of Pearson's correlation coefficient. Baseline readings were recorded for 30 minutes prior to epidural injection. Thereafter, the FECG parameters were recorded for 60 minutes. At delivery, blood samples from umbilical artery were obtained anaerobically for pH and blood gas measurements. Student's t test (paired) was used for statistical analysis ($P<0.05$ significant).

Results. At delivery umbilical artery pH and base excess of all fetuses were within normal limits. When compared with the baseline readings, the values of the 8 FECG waveform parameters recorded after LEA were not significantly different (Tables 1 and 2). However, 7 out of the 10 fetuses showed a change in PR-FHR correlation 5 to 10 minutes after epidural injection. At any given P-R interval, all the seven fetuses had lower heart rate. The magnitude and time course of the change in PR-FHR correlation is shown in Figure 1. This change in PR-FHR correlation was not accompanied by any adverse change in fetal scalp blood pH or base excess.

Discussion. A recent study of the FECG in labor reported that the normal negative correlation between P-R interval and FHR became positive during biochemically proven episodes of fetal hypoxia (4). The occurrence of similar change in PR-FHR correlation without any deterioration in fetal scalp blood pH or base excess following LEA suggests the possibility of a local anesthetic-induced effect on fetal cardiac conduction system.

References.

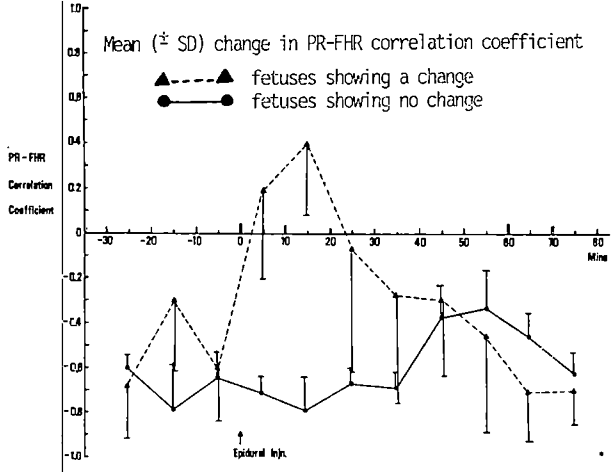
1. Lavin JP. The effect of epidural anesthesia on fetal heart rate monitoring. Clin Perinat 1982; 9:55.
2. Jenkins HML, Symonds EM, Kirk DL and Smith PR. Can fetal electrocardiography improve the prediction of intrapartum fetal acidosis? Br J Obstet Gynaecol 1986; 93:6.
3. Kirk DL. Signal processing of the FECG at Nottingham. J Perinat Med 1986 (in press).
4. Murray H. The fetal ECG: the current clinical developments in Nottingham. J Perinat Med 1986 (in press).

Table 1 Results (mean ± SD) from 7 fetuses which showed changes in PR-FHR correlation.

	Baseline	Post-LEA (0-30 min)	Post-LEA (30-60 min)
FHR (per min)	136.86 (5.00)	132.29 (6.41)	133.77 (6.79)
P wave duration (millisec)	55.27 (10.99)	55.46 (6.95)	55.54 (7.05)
P wave area (units)	94.40 (31.98)	98.96 (29.71)	101.63 (32.39)
P-R interval (millisec)	102.99 (10.39)	105.14 (10.13)	101.32 (18.02)
QRS duration (millisec)	44.46 (3.97)	44.42 (3.93)	44.44 (4.49)
ST segment position (units)	1019.69 (32.42)	1016.79 (33.68)	1019.26 (24.48)
T wave height (units)	59.44 (24.70)	54.62 (28.72)	50.26 (27.14)
R-T interval (millisec)	164.93 (21.3)	168.34 (18.74)	157.97 (14.48)

Table 2 Results (mean ± SD) from 3 fetuses which did not show changes in PR-FHR correlation.

	Baseline	Post-LEA (0-30 min)	Post-LEA (30-60 min)
FHR (per min)	142.43 (6.45)	143.24 (3.63)	139.79 (4.04)
P wave duration (millisec)	67.92 (5.48)	65.46 (5.96)	66.52 (7.54)
P wave area (units)	313.36 (181.66)	280.21 (178.70)	316.51 (181.21)
P-R interval (millisec)	103.15 (6.88)	100.69 (3.58)	104.81 (2.55)
QRS duration (millisec)	44.81 (5.07)	43.25 (3.67)	42.90 (4.11)
ST segment position (units)	1101.07 (103.54)	1058.03 (84.40)	1089.39 (127.84)
T wave height (units)	159.93 (108.98)	142.42 (89.30)	213.53 (168.69)
RT interval (millisec)	160.69 (18.69)	153.19 (14.00)	157.11 (8.27)



Mean (± SD) change in PR-FHR correlation coefficient

Title: INTERMITTENT LOW DOSE N_2O DOES NOT CAUSE MEGALOBLASTIC ANEMIA

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Introduction: Nitrous oxide inactivates the vitamin B_{12} component of the enzyme methionine synthetase. By interfering with folate metabolism and DNA synthesis, megaloblastic hematopoesis in man follows 5-24 hours of continuous exposure, or 18 hours of intermittent exposure over 24 days to 50% N_2O.[1] Continuous exposure to 50% N_2O for 5 days may cause bone marrow aplasia.[1] We wondered if patients who undergo general anesthesia frequently for procedures such as dressing changes or debridements, are at risk for these complications.

Methods: Following subjects' informed consent and approval by the Institutiona Review Board for the Protection of Human Subjects, 14 male normal volunteers not taking medication or vitamins were randomized into 2 equal groups. Each subject received a gas mixture for 30 minutes on a Monday - Wednesday - Friday schedule over 2 consecutive weeks (6 exposures). Seven subjects received 50% N_2O in O_2 (N_2O Group), while 7 subjects received an air-O_2 mixture of .5 F_IO_2 (Air Group). Peripheral blood was drawn before each exposure and one week after the last exposure, and analyzed by a single experienced hematology technologist blinded as to subjects' gas exposure.

Results: Data analyses are complete at this writing for white cell count (WBC, in thousands/microliter), mean red cell volume (MCV, in femtoliters) and neutrophil lobe count (# lobes). Analyses of other laboratory parameters are pending, and will be reported at the meeting. The Table presents mean ($\bar{x}$), and standard deviation (sd) for the first, middle and last blood draw for each of the 3 currently analyzed parameters, as well as the F value from an analysis of variance done on data from all exposures. No statistically significant change was found in any parameter in either group ($p > .05$).

Discussion: We found no evidence of megaloblastic changes in the peripheral blood of normal subjects exposed intermittently to N_2O over 2 weeks. While it could be argued that the healthy population we studied does not mimic the ill patient population undergoing repeated operations, we feel the study's design eliminates the potentially confounding variables of surgery, bone marrow suppression from disease, and concomitant other drugs. Both leukopenia and hypersegmentation (increased lobe counts) occur early in the course of nitrous oxide-induced hematopoetic toxicity, the former within 2 days, and the latter within 5 days of exposure.[2] We conclude that nitrous oxide given in the dosage schedule used does not cause megaloblastic changes detectable in peripheral blood.

TABLE (abbreviations and description in text; $\bar{x} \pm$ sd)

	AIR SUBJECTS			
	1st	MID	END	F
MCV	88.5 ± 4.7	88.9 ± 4.8	88.7 ± 4.8	0.01
WBC	6.8 ± 1.2	7.2 ± 1.9	5.6 ± 0.9	1.08
# LOBES	3.1 ± 0.1	3.1 ± 0.1	3.2 ± 0.1	0.76
	NITROUS SUBJECTS			
	1st	MID	END	F
MCV	87.4 ± 2.3	87.9 ± 3.5	87.9 ± 3.7	0.07
WBC	6.1 ± 1.2	5.8 ± 1.1	5.3 ± 1.0	0.46
# LOBES	3.1 ± 0.1	3.2 ± 0.1	3.1 ± 0.1	0.37

References:

1. Nunn JF, Sharer NM, Gorchein A, Jones JA, Wickramasinghe SN. Megaloblastic haematopoiesis after multiple short-term exposure to nitrous oxide. The Lancet 1982; 1:1379-81.
2. Skacel PO, Hewlett AM, Lewis JD, Lumb M, Nunn JF, Chanarin I. Studies on the haemopoietic toxicity of nitrous oxide in man. Br J Haematology 1983; 53: 189-200.

Title: CHLOROPROCAINE, LIDOCAINE, BUPIVACAINE AND ARTERIAL BLOOD FLOW IN FIBROID HUMAN UTERUS

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Introduction. Lidocaine, bupivacaine and chloroprocaine are widely used local anesthetics (LA) in obstetrical and gynecological anesthesia. It has been reported that fetal bradycardia, severe fetal depression, acute hypoxia, and fetal death assocaited with paracervical block (PCB) using lidocaine are the results of the anesthetic effect carried via the maternal circulatory system (1.2.). Thus, the purpose of this study was to evaluate and compare lidocaine, bupivacaine and chloroprocaine effects on human uterus arteries *in vivo*, during PCB.

Methods. This study was approved by the committee on human research and it was performed in an operating room during a routine abdominal hysterectomy. All patients were admitted for excision of large uterine myomas. Prior to the experimental procedure, informed consent was obtained from each patient. Patients were anesthetized with either halothane or N2O. Preparation of uterine arteries was performed by the attending gynecologist. Blood flow probes (Carolina Medical Electronics) were autoclaved and placed around the uterine arteries. Three one minute control samples were obtained. Then, either lidocaine (1%), bupivacaine (0.25%) or 2-chloroprocaine (2%) 5ml and 10ml increments were injected paracervically (without epinephrine) at the 4 o'clock and 8 o'clock region ipsilateral to the probe. Next, one minute blood flow samples were recorded at 5, 10 and 15 minutes after injection. Then, the hysterectomy assumed its normal course. A total of three groups of patients (5 patients in each group) were used to test each local anesthetic agent. Saline was injected in 2 patients who served as a control group.

Results. As seen in table 1, there were similar findings for the three anesthetic agents: they all produced vasodilation during the first minutes after the injection and then vasoconstriction occurred. It seems that 2-chloroprocaine produced less vasoconstriction on uterine artery. Lidocaine and bupivacaine affected the uterine arterial blood flow in a very similar pattern, although bupivacaine was somehow more potent in this respect. In spite of these observations, the difference between the three anesthetic agents was not statistically significant. If the time was extended over 15 minute period, one may speculate that the differences between the drugs would reach more pronounced statistical significance. However, the mean effect of all three local anesthetic drugs on the blood flow of the uterine artery as compared to the control values reached statistical significance (p 0.05).

Discussion. A number of lines of evidence suggest that local anesthetic agents (LA) can produce either vasodilation or vasoconstriction in different vascular beds (1,3,4). The uterus has a very rich blood supply and thus local anesthetics introduced in the paracervical area would be rapidly absorbed and distributed by vascular network, that is, along the areas of least resistance. In this study, we assessed the blood flow in non-gravid uterine arteries during PCB with LA in total abdominal hysterectomy. Contrary to several observations (1,2,3), we found that lidocaine, 2-chloroprocaine and bupivacaine significantly diminished uterine blood flow during PCB. Direct action of the LA agents on vascular smooth muscle cannot be excluded. All our patients had rather large benign neplasms (fibromyomas). Whether the pathology of the uterus affected reactivity of the arteries remains to be answered.

References.

1. Bormage, P.R.: Epidural analgesia. Philadelphia, W.E. Suanders Co., Publisher (1978)
2. Shnider, S.M., Levinson: Anesthesia for Obstetrics, Williams and Wilkins, Publisher (1979)
3. De Jong, R.H.: Physiology and Pharmacology of Local Anesthesia, Springfield, Ill., Charles C. Thomas, Publisher (1970)
4. Hyman, Al.: J. Pharmacol. EXP. Ther. 174: 487 (1970)

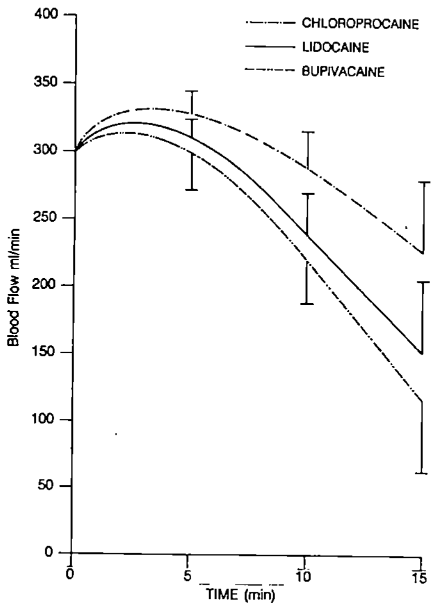

Figure 1. The effect of 2-chloroprocaine, lidccaine and bupivacaine on human arterial blood flow during paracervical block. The starting point (301ml/minute) is the mean ± SEM of the control values.

TITLE: DURATION OF SPINAL ANESTHESIA IN INFANTS UNDER ONE YEAR OF AGE: COMPARISON OF THREE DRUGS

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INTRODUCTION. Although several reports on the use of spinal anesthesia in infants and children have recently been published, little information is available on the duration of analgesia produced by standard doses of the commonly used drugs. We report here a one year's experience with spinal anesthesia in infants using uniform mg/kg doses of three drugs; plain tetracaine, tetracaine with epinephrine, and lidocaine with epinephrine for surgical procedures below the diaphragm.

METHODS. This prospective study was approved by the Institutional Clinical Investigations Committee. During the preoperative interview the parents of 102 infants scheduled for surgical procedures below the diaphragm were offered the choice of either general or spinal anesthesia. Seventy-two elected to have spinal anesthesia, and agreed to participate in the study. Patients were not premedicated. The selection of the appropriate local anesthetic solution for each case was determined according to the anticipated duration of the surgery. Lidocaine 5% containing glucose 7.5% and epinephrine was selected for very short procedures; while plain tetracaine or tetracaine with epinephrine were used for all other cases. The standard dose of lidocaine was 3 mg/kg. The tetracaine dosages were 0.4 mg/kg in conjunction with 0.04 ml/kg of 10% dextrose. If epinephrine was used, the concentration added to both lidocaine and tetracaine was 0.02 cc of a 1:1000 solution. An adult disposable spinal tray was used; supplemented with a 22-gauge x 3.5 cm styleted Quincke needle (standard pediatric lumbar puncture needle) and a 1.0 cc tuberculin syringe. All blocks were performed in the lateral decubitus position, following routine skin preparation with povidone-iodine. Once the adequacy of the level of spinal anesthesia had been established by using either finger pinch or peripheral nerve stimulator set at tetanus to induce a withdrawal response, the infants were lightly sedated with intravenous methohexital 0.5 mg/kg. If the infant began to move to such an extent that the surgical procedure was affected, another dose of intravenous methohexital was used. In all cases the level of sedation was titrated, so that the infant's suck reflex remained intact. In four instances, ketamine 0.25-0.5 mg/kg was used as the intravenous supplement because of the preference of the anesthesiologist involved. Following surgery all patients were transported to the recovery room where they were observed by one of three nurses who were instructed to record the time when the infant first moved his/her toes either spontaneously or in response to non-noxious tactile stimulation. The time from injection of the local anesthetic solution until the first movement of the toes was noted in each case. The duration of neuroblockade produced by the three local anesthetic solutions was compared by analysis of variance.

RESULTS. The infants ranged in age from 37 days to 12 months and weight from 2.7 to 9.6 kilograms. Forty patients received tetracaine with epinephrine, while 22 patients received plain tetracaine. Ten patients received lidocaine with epinephrine. There were no "dry taps" or "bloody taps" in this series. All patients had satisfactory surgical anesthesia. There were no blood pressure or heart rate changes greater than ± 5% from preoperative values. The duration of anesthesia is shown in Table 1. The difference in the duration of block produced by the three drugs was significant ($p < .0001$). Fifty-eight infants received intravenous methohexital, while 10 patients required no supplementation. Only 4 patients received intravenous sedation with ketamine. One vigorous 5 month old infant received 10 minutes of mask nitrous oxide and oxygen for a procedure that outlasted the anesthetic. Atropine was not used in any patient, and no bradycardia was detected. All patients except one of those receiving ketamine were awake, vigorous and able to feed immediately upon entering the recovery room. There were no postoperative complications.

Table 1

Age & Duration of Spinal Anesthesia with Three Different Drugs in Infants (mean ± SEM)

	Lidocaine/ Epinephrine n = 10	Tetracaine n = 22	Tetracaine/ Epinephrine n = 40
age (mos)	6.7 ± 0.6	5.5 ± 0.75	3.9 ± 0.4
duration (min)	56 ± 2.5	86 ± 4	125 ± 3

DISCUSSION. Spinal anesthesia has been shown to be a reasonable option for surgery below the diaphragm in infants under one year of age provided that the anesthesiologist is proficient in the technique and in caring for infants undergoing anesthesia. Special anatomic considerations for this age group include the fact that the spinal cord may end as low as L3 in the neonate. Thus, to be safe, spinal punctures should be performed at the L4-5 or L5-S1 level. Originally, we offered spinal anesthesia to high risk neonates, but soon received so many requests from parents of term infants that we began to offer spinal anesthesia as a routine option. It is of interest that of 102 parents whose children met our criteria for offering the block, 72 chose spinal, 8 chose caudal and 22 chose general anesthesia. Our experience confirmed the reports of others that infants undergoing spinal anesthesia demonstrate no hypotension in spite of the fact that they do not receive intravenous hydration prior to the establishment of the block. We did not use atropine in any patient, and observed no bradycardia.

In conclusion, we have demonstrated that spinal anesthesia is a reasonable option for surgery below the diaphragm in infants under one year of age. We recommend that lidocaine with epinephrine be employed for surgery expected to last less than one half hour, tetracaine be used for surgery anticipated to last one hour and tetracaine with epinephrine be employed for surgery anticipated to last one and a half hours.

Title: PRESERVATION OF CEREBRAL AUTOREGULATION DURING CARDIOPULMONARY BYPASS

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Introduction. The relationship between cerebral blood flow (CBF) and perfusion pressure during cardiopulmonary bypass (CPB) remains controversial.[1,2,3] Since $PaCO_2$ strongly affects CBF during CPB,[4] acid-base management may explain conflicting results. We report changes in CBF produced by experimental elevation of MAP in patients during hypothermic CPB.

Methods. After the protocol was approved by the Clinical Research Practices Committee, eight patients scheduled for elective cardiac surgery gave written consent to take part in this study. Exclusion criteria included hypertension, known cerebrovascular disease, and a requirement for non-protocol drugs before completion of CBF measurements. Fentanyl 75 µg/kg was used to induce and maintain narcosis, adding pancuronium 0.1 mg/kg to facilitate endotracheal intubation. CBF was assessed by clearance of ^{133}Xe (dissolved in saline and injected into the arterial infusion line). Data from 16 cadmium telluride gamma detectors were averaged to obtain global CBF. Mean CBF was calculated by the CBF_{15} technique, corrected for decreases in temperature (temp) and hematocrit (Hct). During nonpulsatile, hypothermic CPB, temp-uncorrected $PaCO_2$ was maintained near 40 mmHg (~ 26 mmHg, corrected for temp = 28°C) by constant in-line monitoring of $PaCO_2$ (Gas Stat^R - American Bentley). Nasopharyngeal temp, CPB flow ($\dot{Q}$), and Hct were also maintained within narrow limits in each patient. Baseline CBF was measured once hypothermic CPB was stable. MAP was then increased by at least 25% by continuous infusion of phenylephrine. In two patients, phenylephrine was not required, since MAP increased spontaneously following the baseline study. All values were expressed as mean ± standard deviation (SD). Mean CBF and MAP data were compared using paired two-tailed *t* tests, significant at $p < .05$.

Results. Controlled variables did not change significantly from baseline to second measurement (Table). In response to a statistically significant increase in MAP, from 53.0±6.8 to 83.8±7.5 mmHg ($p<.0001$), CBF remained unchanged (Fig.). Baseline measurements averaged 15.1±4.1 ml/100g/min. After MAP increased, CBF averaged 14.2±3.6 ml/100g/min.

Discussion. Several authors have analyzed the relationship between CBF and spontaneously occurring changes in MAP during hypothermic CPB; they concluded that, if $PaCO_2$ is maintained near 40 mmHg uncorrected for temp, cerebral autoregulation is preserved.[1,2] Our methodology differed from those studies, since we used each patient as a control, then specifically elevated MAP. Using a similar temp-uncorrected $PaCO_2$ management, we also found that increasing MAP did not change CBF. In contrast, Lundar et al, using transcranial doppler analysis of flow velocity, concluded that autoregulation was impaired or absent when $PaCO_2$ approximated a temp-corrected value of 40 mmHg (~ 56 mmHg uncorrected).[3] The clinical implications of preservation of autoregulation using a temperature-uncorrected acid-base strategy require correlation with cerebral metabolic rate for oxygen, electrophysiologic monitoring, and neuropsychiatric outcome.

References.

1. Govier AV, Reves JG, McKay RD, et al. Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. Ann Thorac Surg 1984; 38:592-600.

2. Henriksen L. Brain luxury perfusion during cardiopulmonary bypass in humans. A study of the cerebral blood flow response to changes in CO_2, O_2 and blood pressure. J Cereb Blood Flow and Metab 1986; 6:366-378.

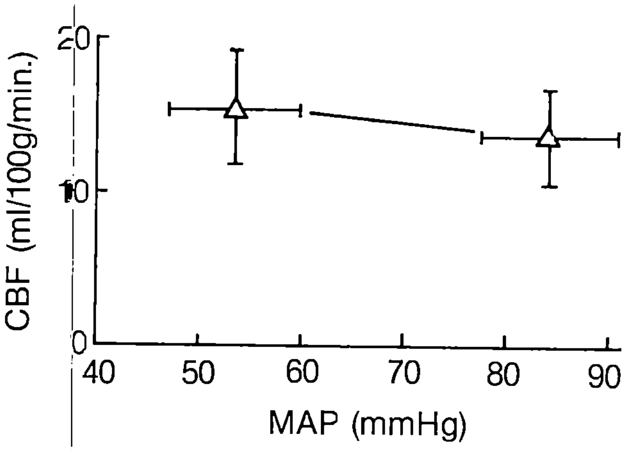
3. Lundar T, Lindegaard K-F, Frøysaker T, et al. Dissociation between cerebral autoregulation and carbon dioxide reactivity during nonpulsatile cardiopulmonary bypass. Ann Thorac Surg 1985; 40:582-587.

4. Prough DS, Stump DA, Roy RC, et al. Response of cerebral blood flow to changes in carbon dioxide tension during hypothermic cardiopulmonary bypass. Anesthesiology 1986, 64:576-581.

Table. Controlled Variables (mean ± SD)

	Temp (°C)	$\dot{Q}$ (L/min/m^2)	$PaCO_2$* (mmHg)	Hct (vol %)
		Group I		
Baseline	26.6±1.4	1.80±0.5	40.8±4.2	24.3±4.1
↑ MAP	26.9±1.2	1.80±0.5	40.9±2.8	24.3±3.6

*uncorrected for body temperature



Title: A COMPARISON OF PROPOFOL AND METHOHEXITAL FOR ANESTHESIA BY CONTINUOUS INFUSION

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Introduction. Propofol (P) is a new agent which has been shown to be safe and effective for induction and maintenance of anesthesia. Recovery is prompt and free from excitatory side effects. Following IV injection, P has a short distribution phase ($t_{\frac{1}{2}\alpha}$ = 2.5 minutes) and a rapid elimination phase ($t_{\frac{1}{2}\beta}$ = 55 minutes). These pharmokinetics make it potentially useful for the induction and maintenance of anesthesia by continuous infusion. This study was designed to evaluate the safety and efficacy of P, compared to that of methohexital sodium (M), for the induction and maintenance of anesthesia, by continuous IV infusion, in surgical procedures lasting 30 to 90 minutes.

Methods. Forty adult patients scheduled for orthopedic or gynecological procedures were studied. The protocol was approved by the IRB and informed consent obtained from all patients. Baseline blood pressure and heart rate were recorded, and an IV premedication of meperidine 1 mg/kg was given 5 minutes prior to induction. Subjects were randomly assigned to receive IV boluses of either P 2.0 mg/kg or M 1.5 mg/kg, followed immediately by an infusion of the same solution, commencing at a rate of 0.1 mg/kg/min. Upon loss of consciousness, succinylcholine 1.5 mg/kg was injected IV, the trachea intubated, and ventilation to an end-tidal CO_2 of approximately 30 mmHg initiated. Muscle relaxation was maintained by pancuronium as necessary. Anesthetic maintenance was augmented by 70% N_2O in 30% O_2 with adjustment of the infusion rate as clinically indicated. Arterial blood pressure, heart rate and EKG were monitored throughout. The anesthetic infusion was stopped 5 minutes before the end of surgery and muscle relaxation reversed. N_2O was discontinued at the end of surgery. The mean infusion rate (total dose divided by time) and the duration of infusion were recorded. Recovery was assessed by measuring the time from the end of surgery until spontaneous eye opening, response to verbal command, and full orientation (able to give correct birth date). Results are presented as mean ± SEM, and the two groups compared by unpaired Student's t-tests, at a significance level of $p < .05$.

Results. Age, sex and weight were not different between the two groups (22 P, 18 M). Induction times to loss of eyelash reflex, were not significantly different (P 53 ± 2 sec, M 48 ± 4 sec). Four patients receiving P and 2 receiving M felt mild pain at the injection site. Hemodynamic changes were significantly different between the groups (Fig I). Over the 5 minute period of induction and intubation, heart rate and systolic and diastolic blood pressures increased significantly more with M than P. During maintenance, despite adjustment of the infusion rate, P produced lower values for heart rate and systolic and diastolic blood pressures, with little change from the preanesthetic baseline values. M produced greater changes in hemodynamic values and two patients briefly exhibited sweating. The duration of infusion was longer with P (81 ± 7 min) than M (65 ± 7 min), but the mean infusion rate for both was similar (P 0.12 ± 0.005 mg/kg/min, M 0.11 ± 0.012 mg/kg/min). Recovery times were not significantly different between the two groups (Fig II). However, with infusions longer than 50 minutes the time to eye opening was more than twice as long with M (19 ± .7 min) than P (7.9 ± .4 min). During recovery, four patients who received propofol had side effects including nausea, confusion, drowsiness and euphoria. Seven patients who received M experienced either nausea, confusion, drowsiness, restlessness or shivering. No venous thrombosis occurred.

Discussion. This study demonstrates that P is a safe and effective agent for induction and maintenance of anesthesia by IV infusion. The lower hemodynamic values with P, during induction and maintenance, contributed to the smoother course and easier control with this agent. Recovery times, although similar for shorter infusions, were greater in the M group when infusions lasted longer than 50 minutes. In addition, the lower incidence of recovery complications with P contributed to its superiority over M for continuous IV anesthesia.

References.

1. Mackenzie N, Grant IS: Propofol ('Diprivan') for continuous intravenous anaesthesia. A comparison with methohexitone. Postgrad Med J 1985; 61(Suppl 3):70-75.

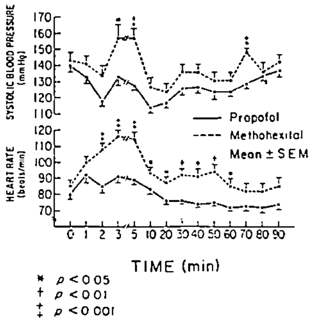

Fig I.
Hemodynamics

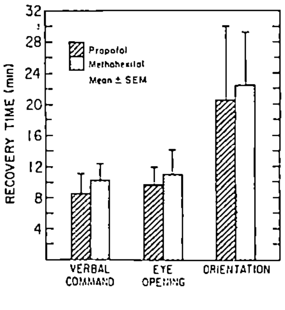

Fig II.
Recovery Time

Title: PHARMACOKINETICS OF SUFENTANIL IN HYPERVENTILATED PATIENTS

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Introduction:

Alterations in drug disposition with hyperventilation have been described for morphine in dogs[1] and fentanyl in humans[2]. This study was designed to determine the pharmacokinetics of sufentanil in hyperventilated neurosurgical patients.

Methods:

Institutional Review Board approval and informed consent from all participating subjects were obtained. Ten patients scheduled for intracranial, spinal or neurovascular surgery were assigned, according to appropriate medical indications, to be either hyperventilated (n=5) or, to serve as controls, ventilated to normocarbia (n=5).

All subjects received metocurine 2mg i.v. prior to induction of anesthesia with thiopental 4-7 mg/kg i.v. Tracheal intubation was facilitated with succinylcholine 1.5 mg/kg i.v. Anesthesia was maintained with N_2O/O_2 (2:1) and sufentanil injected intravenously. Metocurine was given intravenously for muscle relaxation. Esophageal temperature was maintained between 35.2 and 36.6°C with warming blankets.

In the control patients arterial pCO_2 was kept between 40 and 45mmHg. In hyperventilated patients the arterial pCO_2 was maintained between 22 and 28mmHg. Arterial pCO_2 was measured with a Severinghaus electrode at 5 minutes before injection of sufentanil, at 5 minutes after injection and at hourly intervals thereafter. End tidal CO_2 tension was continuously monitored by infrared analysis.

After ten minutes of unaltered ventilation sufentanil 4 ug/kg was injected as an i.v. bolus. Heparinized arterial blood samples were obtained at 1,3,5,10,20,30,45,60 min and at 30 min intervals thereafter up to 240 min. Plasma was separated and frozen until assayed by radioimmunoassay (sensitivity 0.1 ng/ml)[3].

Plasma concentration-time curves from each patient were fitted to both bi- and triexponential equations, using weighted nonlinear least squares regression analysis. The best fit was determined by using the F ratio test. The method of Wagner was used to determine the pharmacokinetic parameters[4].

Comparisons between the pharmacokinetic parameters for the hyperventilated and control patients were made by applying Student's t-test for unpaired data (two-tailed). $P < 0.05$ was considered satistically significant.

Results:

Plasma decay curves for both hyperventilated patients and control patients were best described by biexponential equations.

Hyperventilated: $C = 9.27e^{-.140t} + .618e^{-.00286t}$;
Controls: $C = 12.16e^{-.226t} + 1.11e^{-.0061t}$; where C represents concentration in ng/ml and t is time in min. The pharmacokinetic data are presented in Table 1. The hyperventilated patients had a larger total volume of distribution of sufentanil and a more prolonged elimination half-life when compared to control patients. Linear regression analysis showed a positive correlation between elimination half-life and total volume of distribution ($r = 0.75$, $p < 0.03$). In addition, the intercompartmental rate constant k_{21} was smaller for hyperventilated patients than for controls.

Discussion:

Nishitateno et al reported a decrease in morphine clearance with hyperventilation[1]. In this study, however, the similarity in clearance of sufentanil between the two groups and the positive correlation between elimination half-life and total volume of distribution suggest that the prolongation in drug elimination in hyperventilated patients is due to increased distribution. Sufentanil, with a pKa of 8.0, can exist in vivo as both a free base and an acid salt. The Henderson-Hasselbalch equation predicts that a raised pH, as occurs with hyperventilation, will increase the free base moiety. In addition, Kaufman et al found that for several narcotics an increase in pH results in an increase in drug distribution coefficient (apparent partition coefficient, octanol/water)[5]. These changes could account for both the increased volume of distribution and the decreased k_{21} for sufentanil with hyperventilation. Our kinetic data indicate that sufentanil dosages should be increased in size but reduced in frequency in hyperventilated patients.

Supported in part by a grant from Janssen Pharmaceutica.

References:

1. Nishitateno K, Ngai SH, Finck AD, et al: Anesthesiology 1979; 50:520
2. Cartwright P, Prys-Roberts C, Gill K, et al: Anesth Analg 1983;62:966
3. Michiels M, Hendriks R, Heykants J: J Pharm Pharmacol 1983;35:86
4. Wagner JG: J Pharmacokinet Biopharm 1976; 4:443
5. Kaufmann JJ, Semo NM, Kosh WS: J Med Chem 1975; 18:647

Table 1. Pharmacokinetic Parameters (Mean± SD)

	Hyperventilated,n=5	Control,n=5	<P
$t_{1/2}$ elmin (min)	253±59	119±23	0.005
$t_{1/2}$ dist (min)	5.8±2.9	3.6±1.4	0.1
Clp (ml/min/kg)	14.5±4.4	17.4±2.7	0.4
V_i (L/kg)	0.44±.15	.39±.22	0.4
V_{darea} (L)	5.17±1.31	3.00±.79	0.01
k_{10} (L/min)	.0359±.0132	.058±.0393	0.4
k_{12} (L/min)	.167±.067	.266±.162	0.4
k_{21} (L/min)	.0114±.0048	.0250±.0061	0.005

Title: HEMODYNAMIC EFFECTS OF DOBUTAMINE IN PATIENTS UNDERGOING MITRAL VALVE REPLACEMENT

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Introduction. The hemodynamic effect of dobutamine in postcardiotomy patients with pulmonary hypertension has not been clearly shown before. The purpose of this study was to measure changes in pulmonary artery pressure (PA), pulmonary vascular resistance index (PVRI), and pulmonary shunt flow (Q_S/Q_T) with dobutamine in patients with persistent pulmonary hypertension and increased pulmonary tone in the postoperative period.

Methods. After receiving institutional approval, we studied 10 patients undergoing mitral valve replacement. No changes were made in the usual anesthetic, surgical, cardiopulmonary bypass, or Surgical ICU routine. EKG, systemic arterial pressure, and pulmonary artery pressure were monitored continuously. Left atrial pressure (LA) was monitored in 7 patients and pulmonary capillary wedge pressure (PCWP) in 2. Neither LA nor PCWP was obtainable in 1 patient (he was not included in analysis of PVRI). Arterial blood gas samples were analyzed prior to and at the conclusion of the study. Mixed venous blood gas samples were analyzed in 5 patients. Within 24 hours after surgery, all vasoactive drugs were tapered off and baseline measurements of mean systemic arterial pressure (MAP), HR, PA, LA (or PCWP), central venous pressure, and cardiac output using the thermodilution technique were made. A continuous infusion of dobutamine, 5 µg/kg/min, was begun and increased by 2.5 µg/kg/min every 20 minutes to a final concentration of 10 µg/kg/min. Hemodynamic measurements were recorded after 5, 7.5, and 10 µg/kg/min. Cardiac index (CI), systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI), and Q_S/Q_T were calculated in the customary fashion.

Results. Data were analyzed by paired Student's t test (see Table). The systemic effects of dobutamine were demonstrated in all patients by a significant increase in CI and a decrease in SVRI in a dose-dependent fashion. Of the 8 patients not being artificially paced, HR also increased significantly, actually necessitating stopping the study before the final concentration of dobutamine was given in 5 patients. The effects of dobutamine upon the pulmonary circulation were also notable. Mean PA pressures did not change; however, PVRI decreased significantly in a dose-dependent fashion. None of the patients were hypoxic or hypercarbic during the study period. Though oxygenation was not remarkably affected, dobutamine significantly increased Q_S/Q_T in the 5 patients studied (9.45% ± 3.9 S.D. to 18.35% ± 8.37 S.D., $p<.05$).

Discussion. Dobutamine, a synthetic catecholamine, has been used since 1978 to provide inotropic support in the postcardiopulmonary bypass period. The effect of dobutamine on HR and the peripheral and pulmonary vasculatures is believed to be minimal. This study demonstrated a marked increase in HR in a dose-dependent fashion in all patients studied. The SVRI decreased as CI increased, with no change in MAP, probably due to the reflex withdrawal of vascular tone as perfusion increased, rather than a direct effect. Patients with mitral valve disease oftentimes have persistent pulmonary hypertension after valve replacement, probably due to "fixed" anatomical changes in the pulmonary vessels. Other investigators[1] have failed to show significant changes in PA and PVRI with dobutamine using 5 µg/kg/min in this patient population. The fact that dobutamine significantly increases Q_S/Q_T in this study is supportive of a direct β_2 effect on pulmonary vessels, that is, vasodilating areas of the lung that are not ventilated. This can explain the decreased PVRI and the increased Q_S/Q_T seen in this study.

References.

1. DiSesa VJ, Brown E, Mudge GH, Collins JJ, Cohn LH: Hemodynamic comparison of dopamine and dobutamine in the postoperative volume-loaded, pressure-loaded, and normal ventricle. J Thorac Cardiovasc Surg 1982; 83:256.

Table.

DOBUTAMINE	0	5µg/kg/min	7.5 µg/kg/min	10 µg/kg/min
CI (L/min/m^2)	2.39±.14	3.00±.18^a	3.51±.23^a	3.52±.33^b
HR (beats/min)	71.6±5.2	84.9±5.9^b	83.4±6.6^c	84.3±8.1^b
MAP (mmHg)	74.4±2.5	74.5±2.7	75.1±3.0	73.4±3.4
SVRI (dyne·sec·cm^{-5}/m^2)	2115±111	1755±111^a	1522±110^a	1499±109^b
PA (mmHg)	27.8±2.4	27.2±2.0	29±2.9	26.2±3.7
PVRI (dyne·sec·cm^{-5}/m^2)	353.4±49.1	298.6±58.9^c	277.9±64.5^b	235.6±68.1^c

Values are mean ± SEM.Analysis by paired Student's 't' Test.
^{a} $p<.001$ ^{b} $p<.005$ ^{c} $p<.05$

Title: COMPARISON OF TRACHEAL OXYGEN CONCENTRATIONS USING HUDSON MASK, NASAL CANNULA AND NASAL CATHETER

Authors: Dr. W.F.S. Sellers, F.F.A.R.C.S., C.M.B. Higgs, M.R.C.P.

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Introduction. Three different delivery systems for oxygen were compared in patients with lung disease presenting for diagnostic awake bronchoscopy. Oxygen samples were taken from the trachea.

Methods. Ethical Committee approval and patient consent was obtained for nine patients (mean age 64 years, range 41-74 years) prior to premedication with intramuscular papaveretum and atropine and insertion of ½ inch ribbon gauze soaked with 5% cocaine into both nostrils. A fibre optic bronchoscope was inserted, using 4% lidocaine for nasal, pharyngeal and tracheal anaesthesia and diazemuls was used for patient sedation. A nose-carina length was obtained and after bronchoscopy a metal stylet was left in the trachea over which a 12 gauge Argyle Aero-flo rolled tip suction catheter was passed to rest 5 cm above the carina and fixed at the nostril. A calibrated MS2 mass spectrometer measured oxygen concentrations, a Datex CO_2/O_2 analyser measured carbon dioxide and a Devices recorder charted results. Each patient breathed oxygen at 2 and 4 L/min^{-1} through:

1. Hudson mask (with an extra hole punched in the side for the sampling catheter),
2. Hudson plastic nasal cannula,
3. Argyle 10 gauge oxygen catheter (inserted 8 to 10 cm into the nostril containing the sampling tube).

Delivery systems were used in a random order. When peak inspired oxygen concentration was steady during regular breathing, and with the same end expired CO_2, this peak concentration was used for results. Results were compared for the three delivery systems using Wilcoxon matched pairs signed ranks test.

Results. For each variable performance delivery system there were large differences between patients in peak inspired concentration at each oxygen flow, which can be seen in the individual results in figures 1 and 2.

At 2 L/min^{-1} oxygen the nasal catheter gave best peak inspired oxygen percentage when compared to the nasal cannula ($P<0.02$). There was no difference between nasal cannula and mask and nasal catheter and mask.

At 4 L/min^{-1} the nasal catheter performed best when compared to mask ($P<0.02$) and when compared to nasal cannula ($P<0.01$). There was no significant difference between nasal cannula and mask.

Discussion. In this group of patients with vasoconstricted nasal passages highest peak inspired oxygen concentrations were achieved using a nasal catheter. Different wave forms of oxygen concentration are produced for each delivery system, which makes comparison difficult. The systems are variable performance devices and inspired concentration of oxygen depends on the patients' tidal volume.

At 4 L/min^{-1} oxygen flow over 30% of oxygen is delivered to the trachea, and the systems could be interchangeable to allow for patient comfort, while maintaining adequate tracheal oxygen concentrations. Above 4 L/min^{-1} oxygen flow the nasal catheter becomes uncomfortable.

Figure 1 2 L/min^{-1} oxygen

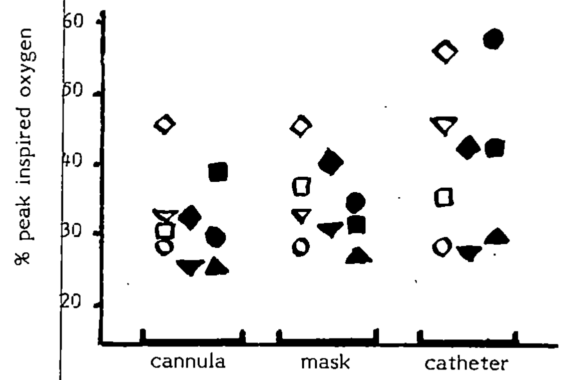
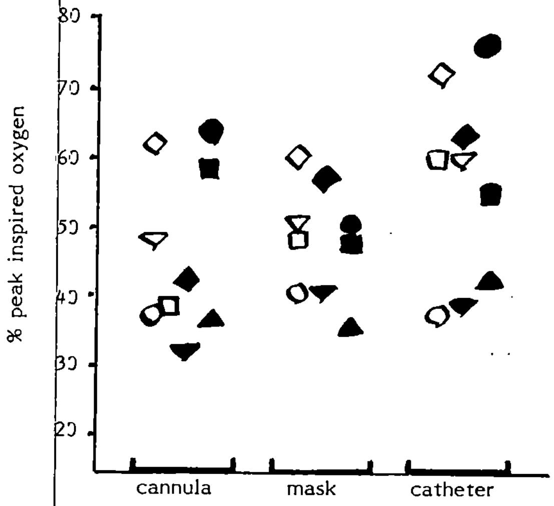


Figure 2 4 L/min^{-1} oxygen



Title: VASODILATION RESULTING FROM MESENTERIC TRACTION IS MEDIATED BY PROSTACYCLIN(PGI_2)

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Introduction: Traction on the abdominal mesentery is associated with decreased systemic vascular resistance(SVR), increased cardiac output(CO) and flushing of the head and neck (1). The mechanism of these hemodynamic and cutaneous findings suggest that they are mediated by the release of hormonal substances. The changes seen are consistent with generation of PGI_2 a potent vasodilator (2) released from the GI mucosa of man (3). We examined the potential role of prostacyclin in the hemodynamic changes associated with traction of the abdominal mesentery.

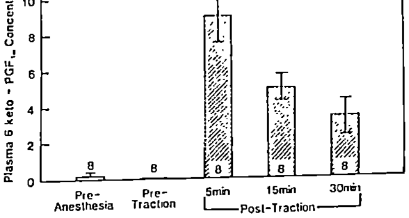
METHODS:Eight ASA Class II-IV patients age 63-79 years were studied after approval of the Institutional Review Board and informed consent was obtained. All patients had a history of hypertension and arteriosclerotic cardiovascular disease. Four patients were receiving beta blockers, and six others were receiving other antihypertensive agents. Patients were premedicated with 0.08 mg/kg of morphine sulfate and glycopyrolate 0.2 mg IM one hour prior to the induction of anesthesia. Intravenous, radial artery and thermodilution pulmonary artery catheters were inserted. Heart rate (HR), systolic, diastolic and mean arterial pressure(MAP), systolic and diastolic pulmonary artery pressure, pulmonary capillary wedge pressure(PCWP), CO and central venous pressure(CVP) were recorded. Fentanyl 4-6 μg/kg IV and thiopental 4-6 mg/kg IV were utilized for induction. Vecuronium 0.08 mg/kg facilitated endotracheal intubation and the patients were ventilated with 60% N_2O in O_2. Isoflurane was administered when clinically indicated by a 20% increase in HR or systemic blood pressure. Mesenteric traction was accomplished by exteriorizing the small bowel and applying retractors to allow exposure of the abdominal aorta. Hemodynamic measurements and 20 ml blood samples were obtained from the radial artery catheter prior to induction, immediately prior to mesenteric traction, and at 5, 15 and 30 minute intervals after the traction. Plasma was analyzed for 6-keto-PGFIα concentration by a radioimmunoassay method (4) Patient's plasma samples were also added to isolated helical strips of cat superior mesenteric arteries precontracted with 200 ng/ml of norepinephrine and the change in developed force was recorded. The stable prostacyclin analog iloprost was used as a reference standard. Single factor ANOVA for repeated measures and Duncan's range test were used to determine the significance of differences among dependent variables. To determine the association between PGI_2 concentrations and SVR or CO, a Pearson correlation coefficient was calculated for each patient and a sign test was applied to the r values. A $P < 0.05$ was considered significant. Data is expressed as mean (± SEM).

RESULTS:Abdominal messenteric traction caused a significant drop in MAP ($p < 0.03$) and SVR ($p < 0.005$) at five minutes post-traction which returned to mean pre-traction values by 30 min. There was also a significant increase in 6-keto $PGF_1\alpha$ concentrations associated with mesenteric traction (Figure 1). There was a significant direct association between CO and 6 keto PGFIα levels ($p < 0.01$) and a significant indirect association between 6 keto PGFIα and SVR ($p < 0.01$). Vasodilation occurred when the 5 minute plasma samples were added to the bathing medium of an isolated cat mesenteric artery preparation which had previously been constricted with norepinephrine. Norepinephrine (200 ng/ml) contracted the cat mesenteric artery strips by 1.56 ± 0.13 grams of developed force in 10 isolated vessels. Control plasma from patients (pretraction sample) decreased developed force by only 0.12 ± 0.11 grams, whereas 5 minute post traction plasma reduced developed force by 0.563 ± 0.092 grams in 6 samples ($p < 0.01$ from control). All patients studied developed erythema and flushing of the skin of the face which coincided with the fall in MAP.

DISCUSSION:We previously demonstrated that the hemodynamic changes associated with traction on the abdominal mesentery resulted from a decrease in SVR with an increased CO.[1] However, we did not examine the basis for the decreased SVR. A humoral mechanism seems to be the cause because every case was associated with flushing of the head and neck which dissipated 30 minutes after the onset of traction and coincided with the return of all hemodynamic variables to pre-traction values. These changes are consistent with generation of prostacyclin (2) since there was a consistent and statistically significant increase in 6-keto-$PGF_1\alpha$ concentration (mean 9.0 ± 1.8 picomoles/ml) which was greatest in all but one patient at 5 minutes after mesenteric traction and decreased to low levels by 30 minutes post traction. There was a significant association between $PGF_1\alpha$ concentrations and CO and SVR. Prostacyclin's role in the hemodynamic response to mesenteric traction is further supported by the in vitro mesenteric artery response to our plasma samples. These denervated isolated arterial strips contract when exposed to norepinephrine (200 ng/ml). This response was significantly reversed by the addition of post traction plasma samples to the system. The response was very similar to that caused by the addition of iloprost (50 ng/ml), a stable prostacyclin analog. Our results are consistent with our earlier hemodynamic findings associated with mesenteric traction, and can now be explained by generation of PGI_2.

REFERENCES

1. Seltzer, et al. Anesthesiology 63:96-99, 1985.
2. Lefer, et al. Science Zoo:52-54, 1978.
3. Ruzsa, et al. FRCS Med Sci 12:528, 1974.
4. Ingerman-Wojenski, et al. J Clin Invest 67:1292-1296, 1981.



Title: AN EMG ANALYSIS OF RHYTHMIC MUSCULAR ACTIVITY DURING RECOVERY FROM ISOFLURANE ANESTHESIA

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INTRODUCTION: Rhythmic muscular activity (RMA) is common after anesthesia. First described following barbituate anesthetics in 1950,[1] it has been observed after every type of general anesthesia. Post-operative RMA is often ascribed to thermoregulatory shivering[2] but this explanation is hard to reconcile with the finding that its incidence is independent of core temperature.[3] RMA has also been attributed to spinal reflexes,[4] pain,[5] sympathetic overactivity, low-dose narcotics, pyrogen release, adrenal suppression, and respiratory alkalosis. The unknown etiology of RMA hampers prevention and treatment. This study was designed to evaluate the hypothesis that there are at least two separate mechanisms responsible for post-operative RMA.

METHODS: With approval from the UCSF Committee on Human Subjects and informed consent, we investigated 9 ASA I or II women [age: 31±8 yr (SD)] who underwent elective laporoscopies or laporatomies. Four received diazepam (5 mg) prior to anesthesia and the others were not premedicated. They were anesthetized with isoflurane/oxygen: barbituates and narcotics were not administered. The patients were extubated "deep" and observed for 100 min during recovery. Every 10 min, we evaluated: 1) the rectal and average skin temperature[6] with Mon-a-Therm thermocouples 2) the end-tidal isoflurane concentration with gas chromatography 3) clinically apparent clonus after plantar flexion on a scale of 0-2 (grade 1 ≤ 5 sec, grade 2 > 5 sec) 4) the patient's sensation of cold or pain 5) clinically apparent RMA on a scale of 0-2 (grade 1 = intermittent muscular activity, grade 2 = continuous activity). RMA was also monitored continuously with surface electrodes on 8 muscles and recorded by a Hewlett-Packard tape deck. EMG signals were analyzed for frequency and bursting pattern with autocorrelation and power spectral density software on a PDP-11 computer. The signals from each muscle were compared with clonus in unanesthetized patients with spinal cord transections (n = 2) and with cold-induced shivering in normal control subjects (n = 7). In patients recovering from anesthesia, a regular, bursting, 6-8 hz activity was considered "EMG clonus" whereas irregular, rapid signals with poorly defined bursts were considered "EMG shivering". Nominal data was compared with χ^2 contingency table; $p < 0.05$ was considered significant.

RESULTS: Fig 1 shows typical EMG signals in: A) normal cold-induced shivering, B) clonus after spinal cord transection, C) RMA early in recovery, D) RMA late in recovery, and E) clinically induced clonus. Fig 2 shows the incidence of clinically apparent RMA, clinically elicited clonus, and sensation of pain and cold plotted against end-tidal isoflurane concentration. Grade 2 clinically induced clonus was more frequently associated with EMG clonus than were grades 0 or 1 ($p < 0.05$). 39% of the muscles monitored showed EMG clonus when grade 2 RMA was detected clinically; this compares with 22% in grade 1 RMA ($p < 0.05$). The incidence of EMG shivering and clonus were independent of both core and average skin temperatures. Pain severity was not correlated with RMA, EMG clonus, or EMG shivering.

DISCUSSION: We observed two distinct patterns of post-anesthetic RMA. One was a rapid, irregular pattern similar to normal cold-induced shivering. The other was slower and regular, with a bursting pattern similar to clonus in patients with a spinal cord transection. This pattern was significantly correlated with grade 2 clinically elicited clonus and with grade 2 RMA. This pattern appears to be a normal emergence phenomenon, probably resulting when descending cortical control does not effectively inhibit normal spinal reflexes. These data suggest that a large fraction of intense post-anesthetic RMA may be spontaneous clonus. Warming measures may not be the most effective prevention or treatment for this muscular activity.

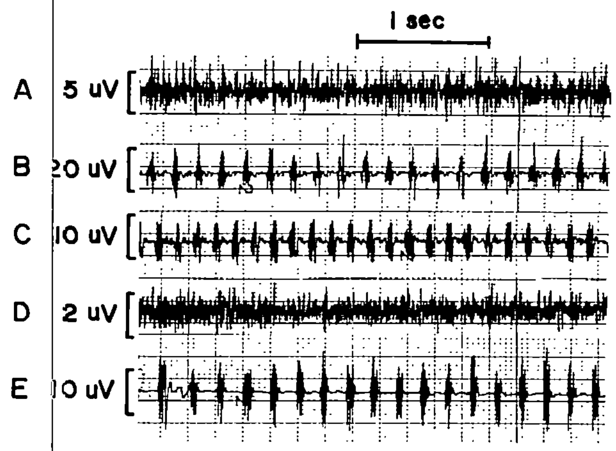

Fig 1: Typical EMG signals from the soleus muscle, in: A) normal cold-induced shivering, B) clonus after spinal cord transection, C) RMA early in recovery, D) RMA late in recovery, and E) clinically induced clonus. The traces shown in panels C,D and E are from the same patient.

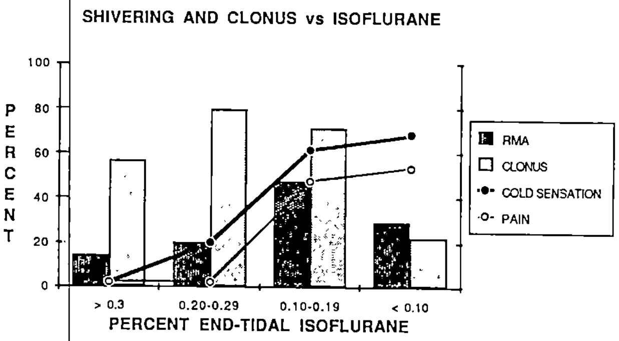

Fig 2: The incidence of clinically apparent RMA, clinically elicited clonus, and sensation of pain and cold plotted against end-tidal isoflurane concentration.

This work was supported by grants from the Pharmaceutical Manufacturer's Association Foundation, O.N.R. grant N00014-84-K-0224, and the UCSF Academic Senate Committee on Research.

REFRENCES:

[1] Bastien J. Quelques remarques sur les anesthesies intra-veineuses prolongees. Anesth et Analg 7:161-165, 1950

[2] Flacke JW, Flacke WE. Inadvertent hypothermia: frequent, insidious, and often serious. Seminars in Anesthesia 2:183-196, 1983

[3] Pausavasdi S, Umpornpukdi S. Post-anesthetic shivering. J Med Ass Thailand 66:212-219, 1983

[4] Soliman MG, Gillies DMM. Muscular hyperactivity after general anaesthesia. Canad Anaesth Soc J. 19:529-535, 1972

[5] Bryce-Smith R. A Review of Fluothane. S.A. Medical Journal. 31:1115-1118 1957

[6] Ramanathan NL. A new weighting system for mean surface temperature of the human body. J Appl Physiol 19:531-533, 1964

Title: CORE TEMPERATURE CHANGES DURING N_2O/FENTANYL AND HALOTHANE/O_2 ANESTHESIA

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INTRODUCTION: Hypothermia during general anesthesia is thought to result from both hypothalamic suppression (i.e. lower thermostatic setpoint) and environmental exposure[1]. Although the relative contribution of each mechanism is unknown, lowering of the setpoint is probably the dominant factor in operations with little environmental exposure. Under these circumstances, temperature might be better maintained with "light" (i.e. N_2O/narcotic) anesthesia than with a potent inhalation gas.[2] Although this was demonstrated in one study,[3] others have not found a difference between the two methods.[4,5] Previous results are difficult to interpret because of poor patient selection,[3] heavy premedication,[3,5] operations with substantial environmental exposure,[3,4,5] and differences in manegment between the two groups.[5] This study was designed to evaluate the effect of two different anesthetic techniques on temperature regulation in patients with minimal environmental exposure.

METHODS: With approval from the UCSF Committee on Human Subjects and informed consent, we investigated 16 ASA I or II subjects [age: 50 ± 16 yr (SD)] undergoing elective eye surgery scheduled to last more than 2 hr. These patients were not premedicated and had no fever, infection, or thyroid disease. All subjects were induced with 4 mg/kg sodium thiopental and 0.1 mg/kg pancuronium. They were randomly assigned to maintenance anesthesia with halothane/oxygen or nitrous oxide (70%)/fentanyl. Halothane concentration was adjusted to maintain an arterial blood pressure 80% of control. The fentanyl group received a loading dose of 5 ug/kg, followed by an infusion of 2-3 ug/kg/hr. All patients were mechanically ventilated to maintain an end-tidal CO_2 concentration between 35-40 mmHg. Fresh gas flow was 5 L/min and a humid-vent® artificial nose was placed in the circut. Warming blankets were not used and the room temperature was maintained at 20.7 ± 1.2 °C. Temperature was measured prior to induction, and every 15 minutes thereafter, with a Mon-a-Therm® thermocouple inserted 10 cm into the rectum.

RESULTS: Fig 1 shows rectal temperature changes during induction and maintenance anesthesia. There were no significant differences between the N_2O/fentanyl and halothane/O_2 groups. In both groups, an initial 0.5°C decrease in the first 30 min was followed by a slow decline (0.15 °C/hr) that continued for 1.5 hr. After 2 hr of anesthesia, there were no further changes in core temperature. The temperature after 2.0 hr of anesthesia did not correlate with patient age.

DISCUSSION: Ophthalmic surgery is ideal for evaluating effects of anesthetics on temperature regulation because it imposes little physiological stress and patients are completely draped. Warm room temperature and airway humidification also helped decrease heat loss in this study. Since environmental exposure was minimal, temperature changes in these patients presumably resulted mainly from direct effects of the anesthetic drugs. The temperature decreased for 2.0 hr in both groups and then stabilized, indicating that the thermostatic setpoint was reached. The equilibrium temperature at 2.0 hr of anesthesia was identical in both groups, demonstrating that halothane/O_2 and N_2O/fentanyl anesthesia have simlar effects on thermoregulation. These data suggest that hypothalamic suppression may be related to MAC rather than anesthetic type.

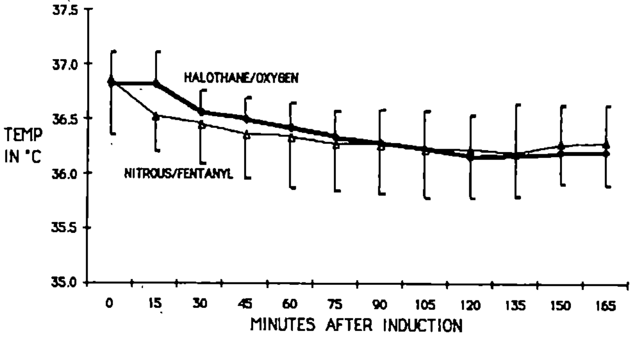

Fig 1: Rectal temperature in patients who received N_2O/fentanyl (Δ, n = 8) or halothane/O_2 (•, n = 8) anesthesia during eye surgery. Time zero is just prior to induction. Each point represents the mean ± standard deviation.

This work was supported by grants from the Pharmaceutical Manufacturer's Association Foundation and the UCSF Academic Senate Committee on Research.

REFERENCES

[1] Flacke JW, Flacke WE. Inadvertent hypothermia: frequent, insidious, and often serious. Seminars in Anesthesia. 2:183-196, 1983

[2] Flacke WJ. Temperature regulation and anesthesia. Int Anesth Clin 2:43-54, 1963

[3] Smith NTY. Subcutaneous, muscle, and body temperatures in anesthetized men. J Appl Physiol. 17:306-310, 1962

[4] Holdcroft A, Hall GM. Heat loss during anaesthesia. Br J Anaesth. 50:157-164, 1978

[5] Tammisto T, Rosenberg P, Elfving G. The effect of anaesthesia and operation on skin and muscle temperature of the lower limbs. Annales Chirurgiae et Gynaecologiae Fenniae. 58:36-41, 1969

Title: POSTPARTUM HYPERREFLEXIA FOLLOWING GENERAL ANESTHESIA IN CESAREAN SECTION PATIENTS

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Introduction. Preeclampsia and eclampsia occur during pregnancy between the 20th week of gestation and the first 24 hours postpartum(1). They remain among the major causes of maternal morbidity and mortality. In the case of eclampsia, hyperreflexia often precedes the convulsion and requires magnesium sulfate therapy. However, hyperreflexia is also common in the early postanesthetic period following general anesthesia in surgical patients(2,3). Therefore, hyperreflexia in obstetric patients who have undergone general anesthesia can present a problem of differential diagnosis; is this hyperreflexia a manifestation of preeclampsia requiring treatment with magnesium sulfate, or is this merely a transient manifestation from general anesthesia? This study was undertaken to examine the incidence and time course of such abnormal reflexes in preoperatively normotensive parturients undergoing general anesthesia for cesarean section.

Methods. Forty-five parturients(n=45) undergoing general anesthesia for cesarean section were studied. On admission to the labor and delivery suite, informed consent was obtained, and preoperative evaluations of blood pressure(BP), patellar tendon reflex, ankle clonus and urinalysis were performed. General anesthesia was induced with thiopental and succinylcholine using a rapid sequence induction technique, and maintained with nitrous oxide, oxygen and 0.5-0.75% enflurane. When there was evidence of neuromuscular recovery from succinylcholine, d-tubocurarine was given. After the infant was delivered, anesthesia was supplemented with fentanyl, and enflurane was discontinued. Neuromuscular blockade was reversed with a mixture of neostigmine and glycopyrrolate, and adequacy of the reversal was confirmed by the ability of the patient to sustain head-lift for more than 5 seconds. BP, patellar reflex and ankle clonus were evaluated at 10 minutes after extubation, and thereafter every 30 minutes for the first 2 hours in the recovery room. Morphine sulfate was administered for postoperative pain relief as needed. Hypertension was defined as a systolic BP >140 torr or diastolic BP >90 torr, measured by Dinamap. Patellar reflex was graded as follows; 0: absent, 1+: hypoactive, 2+: normal, 3+: increased, 4+: marked hyperactive with clonus. Ankle clonus was graded by the number of beats of clonus observed, and the clonus was considered sustained when there were more than ten beats. The perioperative values of BP, incidence of hyperreflexia and ankle clonus, and the time course of such reflexes were tabulated and analyzed.

Results. Mean maternal age was 29 years and mean gestational age was 38 weeks. The major indications for cesarean section were fetal distress, previous cesarean section and dystocia. Preoperatively, all patients were normotensive and mean BP was 119±12/72±8 torr. Values of patellar reflex were as follows: 1+ = 10 patients, 2+ = 31 patients and 3+ = 4 patients. No ankle clonus was elicited in any patient. None of the patients showed significant proteinuria (>1+). At 10 minutes postextubation, the mean BP was 132±18/76±14 torr, and hypertension was noted in 15 patients (33%). A hyperactive patellar reflex (>3+) was noted in 27 patients (60%), and ankle clonus was elicited in 30 patients (66%) with sustained clonus in 11 patients (see table). At 120 minutes postextubation, hyperreflexia had resolved spontaneously in most patients. No sustained ankle clonus was elicited. However, one patient required magnesium sulfate therapy for hypertension (150/110 torr) and persistent hyperreflexia (3+ patellar reflex) 6 hours postpartum.

Discussion. Mild to moderate hypertension and hyperreflexia including ankle clonus were commonly noted in the immediate post-anesthesia period among uncomplicated obstetric patients who had undergone general anesthesia. Hypertension and hyperreflexia resolved without specific treatment in a few hours in most patients. This hyperreflexia appears to reflect transient physiologic changes attributable to extubation, emergence from general anesthesia and pain. Therefore, magnesium sulfate therapy may not be indicated for such hyperreflexia in the early postanesthetic period unless the hyperreflexia is persistent and associated with other signs of preeclampsia, such as persistent hypertension or/and significant proteinuria.

References.

1. Pritchard JA, Stone SR: Clinical and laboratory observations on eclampsia. Am J Obst & Gynec 1967;99:754-763
2. Rosenberg H, Clofine R and Bialik O: Neurologic changes during awakening from anesthesia. Anesthesiology 1981;54:125-130
3. Soliman MG, Gillies DMM: Muscular hyperactivity after general anesthesia. Canad Anaesth Soc J 1972;19:529-535

TABLE: PERIOPERATIVE VALUES OF BP, PATELLAR REFLEX AND ANKLE CLONUS

	PREOP	POSTOPERATIVE			
		10min	30min	60min	120min
SYSTOLIC BP	119±12	132±18	128±14	127±11	122±12*
DIASTOLIC BP	72±8	76±14	72±10	76±6	70±10*
PATELLAR REFLEX (n=45)					
1+	10	6	8	7	8
2+	31	12	14	22	29
3+	4	21	22	16	8
4+	0	6	1	0	0
ANKLE CLONUS (n=45)					
NONE	45	15	19	27	37
2-10 BEATs	0	19	16	15	8
SUSTAINED	0	11	10	3	0

* Mean Values ± 1 SD

Title : INFLUENCES OF HALOTHANE AND ISOFLURANE ON BAROREFLEX CONTROL OF VASCULAR CAPACITANCE IN THE DOG

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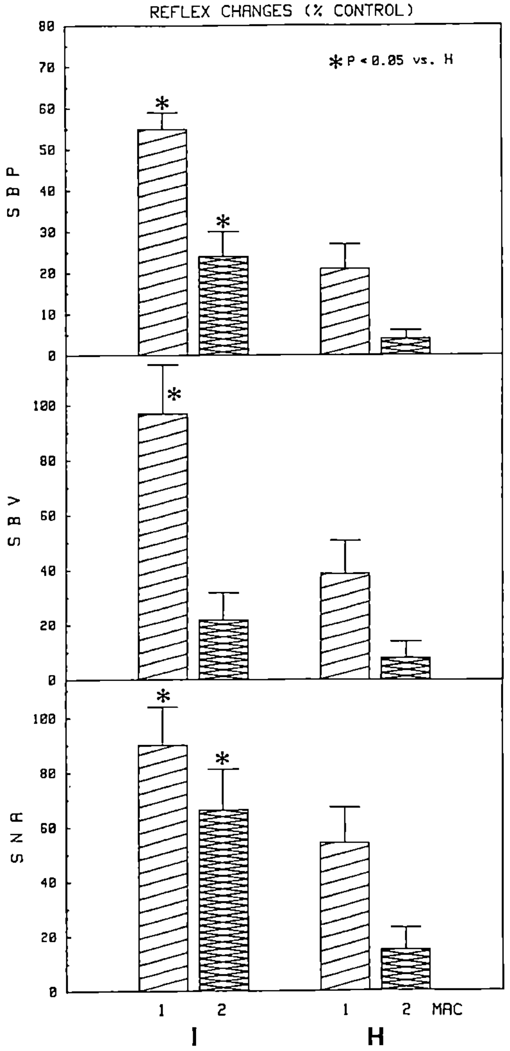
Introduction. The venous system contributes importantly to control of circulation. A small change in venous capacitance may alter venous return to the heart. It has been shown that halothane (H) and isoflurane (I) depressed baroreflex control of heart rate, vascular resistance and sympathetic nerve activity (SNA)[1]. However, the influence of H and I on baroreflex control of venous capacitance is not known. The purpose of this study is to examine the effects of H and I on carotid sinus baroreflex control of vascular capacitance, vascular resistance and SNA in systemic circulation of the dog.

Methods. Fourteen mongrel dogs (20-30kg) were anesthetized with sodium pentobarbital, intubated and mechanically ventilated. The left carotid sinus (CS) was vascularly isolated and perfused by a pump to permit rapid changes in CS pressure (CSP). The right CS was denervated and a bilateral vagotomy was performed. Cardiopulmonary bypass via a reservoir oxygenator was accomplished after median sternotomy. Reflex changes in vascular capacitance were assessed by changes in systemic blood volume (SBV) which were obtained by measuring changes in venous return at constant cardiac output and constant central venous pressure. Venous return from the inferior vena cava, superior vena cava and right ventricle was measured using a Biotronix electromagnetic flow meter and probes. The left ventral ansa subclavian nerve was isolated to permit recording of efferent SNA. H and I (0.5, 1.0, 2.0 MAC) were added in the gas to the oxygenator. Arterial blood gases were maintained at $PaO_2>200$ mmHg and $PaCO_2$ 30-40 mmHg. Changes in systemic blood pressure (SBP), SBV and SNA were obtained by increasing or decreasing CS pressure between 50 and 200 mmHg.

Results. H (0.5, 1.0 and 2.0 MAC) decreased SBP by 15±4, 26±5, and 41±5 mmHg (mean±SD), respectively. I (0.5, 1.0 and 2.0 MAC) decreased SBP by 12±7, 20±9 and 35±5 mmHg, respectively. Increasing CSP caused decreases in SBP by 15-40 mmHg and increases in systemic SBV by 54-235 ml. The figures show reflex changes of SBP, SBV and SNA produced by increasing CSP from 50 to 200 mmHg at the level of 1 and 2 MAC of H and I. Both H and I depressed reflex changes of SBP, SBV and SNA at 1 and 2 MAC compared to control. The depression of reflex changes of SBP elicited by 1 and 2 MAC of H was greater than that by I ($p<0.05$, non-paired t-test). Reflex changes of SBV were greater in 1 MAC of I than 1 MAC of H ($p<0.05$). The reflex change of SNA at 2 MAC of I was well preserved compared to that of the SBP and SBV.

Discussion. The results of this study indicate that both H and I depress baroreflex control of vascular capacitance as well as those of vascular resistance and SNA. 1 MAC of H is more depressant on baroreflex control of vascular capacitance than 1 MAC of I. Although 2 MAC of H and I almost abolished baroreflex changes of vascular capacitance and resistance, I preserved baroreflex responses of SNA. This difference between vascular and SNA responses may be accounted for by direct action of I on the vascular smooth muscle. In conclusion, this study suggests that H and I depress baroreflex control of vascular capacitance and resistance. This depression may be caused by decreased responsiveness of vascular smooth muscle in addition to depression of the central nervous system.



Reference.
1. Seagard JL, Bosnjak ZJ, Hopp FA, Kotrly KJ, Ebert TJ and Kampine JP. Cardiovascular effects of general anesthesia. In: EFFECTS OF ANESTHESIA, Waverly Press, Baltimore, 1985, pp 149-177.

Title: A COMPARISON OF OXYMORPHONE AND FENTANYL AS NARCOTI SUPPLEMENTS TO GENERAL ANESTHESIA

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Introduction. Oxymorphone and fentanyl are potent, semi-synthetic narcotic analgesics that provide excellent analgesia, hemodynamic stability and negligible histamine release when used in general anesthesia. While fentanyl's short plasma half-life is appropriate for brief surgical procedures, relatively large amounts of drug are required in the longer case. Under such circumstances, the prolonged duration of oxymorphone may substantially reduce the need for repeated dosing. Provided that efficacy and safety profiles are comparable, a significant oxymorphone cost-advantage may be proportional to total case length. We present preliminary results of a carefully documented comparison in which a global peri- and postoperative assessment determined the actual efficacy, safety, and cost effectiveness of each agent.

Methods. Following institutional approval, written informed consent was obtained from thirty patients (ASA PS 1-3) undergoing elective gynecological procedures with an anticipated duration of over two hours. Patients were randomized into two treatment groups following premedication with diazepam 0.1 mg/kg p.o. Based on a potency ratio of 10:1, patients received either fentanyl 7 mcg/kg or oxymorphone 70 mcg/kg in a blinded fashion prior to thiopental/succinylcholine induction and laryngoscopy. Anesthesia maintenance included nitrous oxide and pancuronium, while additional narcotic administration (fentanyl 50 mcg, oxymorphone 500 mcg) and vol % inspired isoflurane was administered at the discretion of a blinded anesthesiologist.

Hemodynamic/respiratory measurements were precisely documented every 2-4 minutes using the Datascope Datatrac^R automatic chart recorder. Average vol % inspired and MAC minutes isoflurane were calculated from the trends generated by a Perkin-Elmer mass spectrometer. Total drug use, assessment of the quality of induction, perioperative hemodynamic stability, and quality of emergence were assessed. This evaluation continued into the recovery period where degree of respiratory depression, pain, and total recovery stay were documented.

Data were analyzed with three-way analysis of covariance. P values less than 0.05 were considered statistically significant. Results are expressed as mean ± S.E.M.

Results. Analysis of oxymorphone (n=13) and fentanyl (n=17) groups revealed no significant differences in patient age, height, or weight. Table 1 summarizes anesthetic, reversal, and postoperative analgesic requirements in relation to case length.

Table 1.

	Long Case (>120 min)		Short Case (<120 min)	
	(n = 11) Oxymorphone	(n = 13) Fentanyl	(n = 2) Oxymorphone	(n = 4) Fentanyl
Length nesth. (min)	193±13.7*	161±8.5	117±1.0*	99±3.9
Total I duction (ml)	6.7±.4	6.5±.3	5.3±.4	6.5±.2
Total M intenance (ml)	4.7±1.2*	7.2±1.1	6.2±1.7	2.9±.7*
Total m kg	.17±.01*	.22±.02	.23±.05	.15±.01*
MAC min Forane	60.5±7.2	57.3±5.5	45±10	43.8±7.7
Ave Fra tion Expired Vol %	.36±.04*	.40±.03	.43±.10*	.48±.06
Total N rcan (ug)	25.4±9.8*	12.3±6.9	160±40*	10±1.0
Total M rphine Dose Recover Analgesia (mg)	1.3±.5	2.7±1.0*	0±0	4.5±2.0*

(* significant p<.05)
Results expressed as mean ± S.E.M.

In long anesthetic cases, significantly less study drug was required in the oxymorphone group (.17 cc/kg) as compared with patients receiving fentanyl (.22 cc/kg); however, the reverse is true in the shorter cases.

The amount of volatile anesthetic required to achieve hemodynamic stability was significantly reduced in the oxymorphone group even though total case length was longer.

Overall quality of induction, maintenance, and postoperative analgesia was judged superior overall in the oxymorphone group (decreased incidence of hypotension and chest wall rigidity, decreased maintenance administration, and PAR morphine requirements).

In contrast, speed of reemergence was more rapid and less naloxone was required in the fentanyl group, especially in cases less than 120 min. Observer assessment of these findings suggested superior oxymorphone efficacy in long cases while safety (as judged by respiratory depression and total naloxone requirement) was lessened in the shorter procedures.

Discussion. The hypothesis that smaller amounts of an opioid having a long duration of activity might provide a more cost effective adjunct in general anesthesia than larger amounts of a short acting agent was tested in patients undergoing similar procedures with the same volatile anesthetic. Hemodynamic stability was reliably achieved with either agent; however, in the longer procedures, an increased amount of maintenance narcotic, volatile anesthetic, and recovery room analgesic was required in the fentanyl treated group.

In summary, oxymorphone is a safe, efficacious, cost effective alternative to fentanyl in the longer operative procedure; however, increased naloxone requirements and longer recovery room stay suggest that fentanyl is the superior agent in the shorter case.

Title: THE PHARMACOKINETICS OF SUSTAINED-RELEASE MORPHINE TABLETS AND ORAL MORPHINE SOLUTION: A MULTICENTRE DOUBLE-BLIND CROSSOVER TRIAL.

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Introduction: Morphine solution administered orally 4 - hourly has been shown to be effective in controlling the chronic pain of advanced malignant disease (1). Sustained release morphine tablets have been used clinically for a few years (2) however there is limited pharmacokinetic data on the sustained release morphine tablets, and no controlled study has been conducted in patients with chronic cancer pain. The purpose of this study was to define and compare the steady-state pharmacokinetics of sustained release morphine sulphate tablets (SRMT) to oral morphine sulphate solution (MSS) at clinically effective doses in patients with chronic, severe pain of cancer origin.

Methods: Following institutional approval and after obtaining informed consent 15 patients (8M & 7F) from 3 hospitals, aged 48-86 years (mean=59) with chronic pain due to cancer requiring opiates were included in the study. Patients with hepatic or renal insufficiency were excluded from the study, as were patients with intractable nausea & vomiting, or uncontrolled pain. The study followed a two-period, double-blind, randomized crossover trial design. Each patient completed both phases of the trial, with each phase lasting 5 to 7 days. Patients were randomly allocated to start the first treatment period with either the SRMT and placebo elixir, or the oral MSS and placebo tablets. At crossover patients then took the alternative test medication and the appropriate placebo for the second period.

The daily dose of morphine was individualized and equivalent daily doses of SRMT and MSS were administered during the active phase for each preparation. Morphine solution was given every four hours, and SRMT's were given 12-hourly. No other opiods were administered during the course of the study. On the last day of each period, when a steady-state level of morphine was achieved, venous blood samples were collected through an indwelling catheter just before 10 AM. dosing, and every 30 min. thereafter through a 12 hour time interval. The plasma morphine concentration was determined using high performance liquid chromatography, allowing separation of morphine from morphine metabolites

Results: All patients obtained good analgesia. The daily dose of morphine ranged from 60 to 400 mg. per day (mean=155 mg., 0.82-6.56 mg/kg/day). The mean plasma concentration-time curve for SRMT and MSS are shown in Fig. 1. The area under the time-concentration curve (AUC) was calculated for each patient using the trapezoidal rule. The mean plasma morphine level (MPL), the minumum morphine concentration (C. MIN), the maximum morphine concentration (C. MAX), and the ratio of minumum to maximum morphine concentration were calculated (C MIN/C. MAX) and the results summarized on Table 1. There was no significant difference between the tablets and solution with regard to oral bioavailability based on AUC, MPL, or C. MAX. The time to maximum concentration (T. MAX) was significantly shorter ($p<0.002$) for morphine solution (1.2±0.6 H) than for the sustained-release preparation (3.6±2.4 H.). The C. MIN/C. MAX ratio just reached statistical significance between preparations.

Discussion: The sustained-release morphine tablet provided sustained plasma morphine levels and effective analgesia over a 12 hour dosing interval in patients with chronic malignant pain. This preparation is a useful alternative to the standard morphine solution, particularly in the ambulatory patient in whom a longer dosing interval is desirable.

References:

1. Melzack R, Ofiesh JG, Mount BM. The brompton mixture: effects on pain in cancer patients. Can Med Assoc J 1976;115:125-29.

2. Leslie ST, Rhodes A, Black FM. Controlled release morphine tablets-a study in normal volunteers. J Clin Pharmacol 1980; 9.531-4.

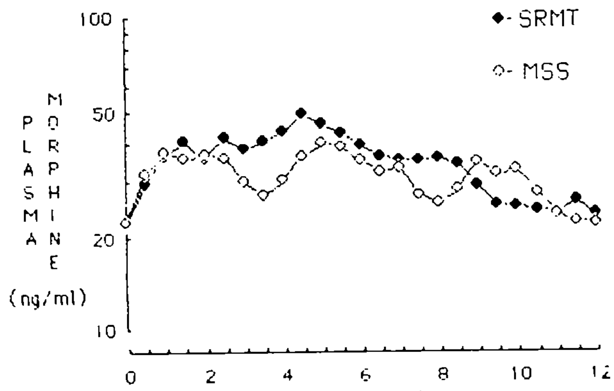

Fig 1 Mean plasma morphine concentration versus time curve for all patients during a 12 hour dosing interval at steady-state

Table 1. PHARMACOKINETIC DATA (ALL PTS.) - MEAN ± ST. DEV.

	SRMT	MSS	
AUC_{0-12} (ng/ml)	419±365	379±269	NS
M.P.L. (ng/ml)	34±30	31±22	NS
T.MAX (H.)	3.6±2.4	1.2±0.6	P< 0.002
C. MAX (ng/ml)	65±45	55±31	NS
C. MIN (ng/ml)	14±17	16±15	NS
C. MIN/C. MAX	0.19±0.10	0.25±0.12	P< 0.04

EPIDURAL FENTANYL FOR RELIEF OF LOWER EXTREMITY TOURNIQUET PAIN IN ORTHOPEDIC SURGERY

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INTRODUCTION:

Many operative procedures of the extremity are performed with a pneumatic tourniquet under regional anesthesia. However an intense burning pain develops at the tourniquet site 45-60 minutes after its inflation.[1] Various techniques have been used to treat this pain, but with little success.[2,3] It is only relieved by deflation of the tourniquet. Mediation of this pain cannot be explained on the basis of the anatomical pathways as it occurs despite profound surgical anesthesia. Peripheral sympathetic afferent C-fibers which terminate in the substansia gelatinosa of the spinal cord carry the unpleasant sensation of tourniquet pain.[3] The proposed transmitter at this primary synapse is substance P. Activation of C-fibers releases substance P. Opiates injected into the epidural or intrathecal space inhibit the release of substance P.[4] Therefore, it is possible that an opiate administered in the epidural space may alleviate lower extremity tourniquet pain.

This study was done to assess the effect of epidural fentanyl on lower extremity tourniquet pain when such pain develops in the presence of epidural anesthesia. Fentanyl was selected because of its greater dural permeability, faster onset, and shorter duration of action.[5] Respiratory depression has not been reported with epidural fentanyl.

METHODS:

The study was approved by the Institutional Review Board. 14 ASA Class I patients between the ages 18-60 years undergoing knee or ankle surgery were randomly selected from the elective orthopedic surgery schedule. Surgical procedures required the use of a tourniquet. Tourniquet pain was discussed with the patients preoperatively. The study was double blinded and divided into two groups. Following the development of tourniquet pain, one of the test solutions was injected through the epidural catheter.

Group I: Received 10 ml of preservative free normal saline.

Group II: Received (100 µg) 2 ml of fentanyl in 8 ml of preservative free normal saline.

All patients were premedicated with 10 mg of oral diazepam and received 10 ml/kg Ringer's lactate solution intravenously prior to the epidural anesthesia. Vital signs were monitored. Continuous lumbar epidural anesthesia was established using 2% xylocaine with 1:200,000 epinephrine. The epidural catheter was placed and secured. Subsequent dosages of local anesthetic were injected through the epidural catheter. Anesthesia to pinprick was established up to T_4 dermatome. The extremity to be operated upon was exsanguinated with an Esmarch bandage and the tourniquet was inflated to 350 mmHg. Changes in the vital signs, total tourniquet time, and onset of tourniquet pain were recorded. Test solutions were injected through the epidural catheter when patients complained of tourniquet pain. Persistence of pain 5-10 minutes after the injection necessitated induction of general anesthesia for completion of surgery. All patients were observed in the recovery room until the effects of the epidural anesthetic had dissipated and they complained of pain at the surgical site. Preliminary results are reported.

RESULTS:

Table 1 represents mean and standard deviations for age and weight. Table 2 represents mean and standard deviations for onset of tourniquet pain and total tourniquet time.

Table 1

Group	N	Age (Yrs)	Weight (Kg)
Saline	4	32.4 ± 13.8	78 ± 10.3
Fentanyl	6	31.1 ± 7.4	70.4 ± 9.5

Table 2

Group	N	Onset of Pain (minutes)	Total Tourniquet Time (minutes)
Saline	4	61.2 ± 21.5	88.2 ± 17.9
Fentanyl	6	63.8 ± 19.5	109.4 ± 28.6

None of the patients who received saline through the epidural catheter had any relief of tourniquet pain and all required general anesthesia. Five out of six patients who received fentanyl through the epidural catheter had adequate relief from pain. One patient in the fentanyl group developed pruritis and was treated with diphenhydramine. Postoperatively no patients developed nausea, vomiting, urinary retention, or respiratory depression.

Three patients in the control group and one patient in the fentanyl group were excluded from the study. One had an intravascular injection of local anesthetic through the epidural catheter and surgery was completed under general anesthesia. In the other three patients tourniquet time was less than 45 minutes.

DISCUSSION:

Clinical experience has shown that sensory blockade up to T_4 dermatomal level with local anesthetic alone neither treats nor prevents tourniquet pain. Until now the treatment of tourniquet pain has met with little success. Opiates administered alone in the epidural space produce inadequate anesthesia for surgery. Therefore, patients undergoing prolonged operative procedures with a tourniquet on the lower exremity are given a general anesthetic. This study shows that 100 µg of fentanyl injected epidurally is effective in the treatment of tourniquet pain which occurs despite adequate surgical anesthesia. Epidural anesthesia with a combination of xylocaine and fentanyl will allow these procedures to be done free of tourniquet pain. No interaction has been reported between xylocaine and fentanyl administered in the epidural space. The technique seems promising and further study is continuing. Development of delayed complications following epidural opiates is a possibility though none occurred in the ten patients studied.

REFERENCES:

1. Cole F: Tourniquet pain. Current researches in Anesth & Analg 31:63-64, 1952
2. Rosenblatt RM, Hetherington A: Failure of transcutaneous electrical simulation to alleviate experimental tourniquet pain. Anesth & Analg 60:720-722, 1981
3. Egbert LD, Desas TC: Cause of pain from a preumatic tourniquet during spinal anesthesia. Anesthesiology 23:287-290, 1962
4. Yaksh TL: Spinal opiate analgesia: Characteristics and principles of action. Pain 11:293-346, 1981
5. Moore RA: Dural permeability to narcotics: in vitro determination and application to extradural administration. Br J Anaesth 54:1117-1128, 1982.

Title: *IN VITRO* RESPONSE TO HALOTHANE OF HUMAN PLATELETS IN MALIGNANT HYPERTHERMIA

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Introduction. Malignant hyperthermia (MH) is a genetic disorder in which halogenated anesthetics and succinylcholine can trigger rhabdomyolysis as a consequence of rigor of the skeletal muscles. This abnormality can be diagnosed in the affected individuals by muscle biopsy and halothane and/or caffeine contracture test with good selectivity and sensitivity.[1,2] The conduct of this essay, however, is time consuming and expensive.

Methods. Freshly obtained platelets of 5 known M.H. probands, their relatives and normal volunteers were exposed to 2.5% halothane in a platelet rich concentrate and the ATP, AMP and hypoxantine content were measured as previously described.[3] The morphologic changes of platelets of these individuals was also studied by the method of Basrur et al.[4]

Results and Discussion. *In vitro* exposure to halothane of platelet-rich plasma from M.H. patients results in a significantly altered nucleotide profile as measured by HPLC. Computer-assisted 3-D reconstructions of serial thin sections reveal loss of the microtubular band, rounding of the cells, marked degranulation, extreme dilation of the open (surface-connected) canalicular membrane system (OCS), and probably cytoplasmic contraction. Platelet aggregation and the formation of microvillar projections do not occur. All described changes are absent from control platelets after exposure to halothane. (see fig 1 &2). These morphological observations resemble those seen in M.H. susceptible pigs exposed *in vivo* to halothane. Similar disturbances of EM morphology occur when intracellular calcium distribution is experimentally altered.[5] Degranulation and dilation of the OCS in platelets from M.H. patients are results consistent with release of calcium from membrane-limited compartments into the ground substance. They always correlate with a significantly altered nucleotide profile, are irreversible, and are interpreted as corresponding to a state of rigor in muscle. The use of platelets as a model for the study of M.H. is supported by the EM findings.

References.

1. Rosenberg, H., Reed, S.: *In vitro* contracture tests for susciptibility to malignant hyperthermia. Anesth. Analg., 1983; 62:415-20.
2. Rosenberg, H., Reed, S., Heiman, T.; Masseter Spasm, Rhabdomyolysis and Malignant hyperthermia. Anesthesiology; 1980; 53:S248.
3. Solomons and Masson; Acta Anaesthesiol. Scand., 1984; 28:185.
4. Basrur et al: Scanning Electron Microscopy, 1983, pp 209.
5. Worner et al. J. Ultrastruc. Res., 1981, 75:259.

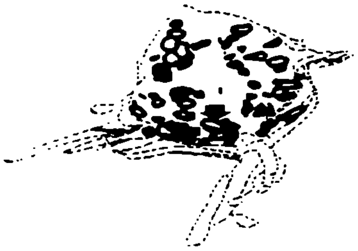

FIGURE 1. NORMAL PLATELET EXPOSED TO HALOTHANE

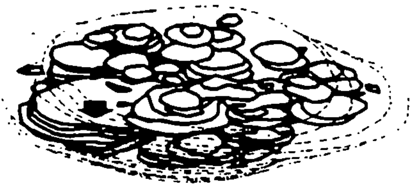

FIGURE 2. M H PROBAND'S, PLATELETS (SWISS-CHEESE) PLATLETS.

Title: SUCCINYLCHOLINE DOES NOT CONTRIBUTE TO POSTOPERATIVE PAIN AFTER OUTPATIENT LAPAROSCOPY

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Introduction: It has been suggested that because of its well known association with postoperative pain (PP) in ambulatory patients, succinylcholine (SDC) should not be used for these cases. Although Pearce et al. (1) stated that atracurium (ATR) is a good alternative to SDC for outpatients, Collins et al. (2) have shown that 79.6% of ambulant laparoscopy patients complained of PP even when SDC was not used. We sought to determine if ATR or vecuronium (VEC) offered any advantage over SDC for the prevention of PP, sore throat and the need for analgesics.

Methods: After approval by our Human Studies Research Committee, 35 ASA Class I or II females undergoing outpatient laparoscopy were selected. All patients received fentanyl 50-150 µg and glycopyrolate 0.2 mg when their IV's were started, and were randomly assigned to 3 groups. After induction with thiopental, Group 1 (n=9) received 0.40 mg/kg ATR; group 2 (n=13) received 0.08 µg/kg VEC and Group 3 (n=13) received SDC 1 mg/kg followed by a SDC infusion. The investigators were blinded as to the relaxant given. All patients underwent endotracheal intubation with unlubricated styletted tubes. Oropharyngeal airways and esophageal stethoscopes were used when judged clinically necessary. Anesthesia was maintained with an inspired concentration of up to 1.2% isoflurane in 70% N_2O/30% O_2. Groups 1 and 2 were reversed with neostigmine 0.04 mg/kg and glycopyrolate 0.5 mg after surgery. Patients were contacted on the day after surgery by an investigator blinded to the relaxant used. Analgesic usage and complaints of pain and sore throat were determined. The data were analyzed by ANOVA and Fisher's Exact Probability Test. A $P < 0.05$ was considered significant.

Results: The results of the study are summarized in Table 1. There were no significant differences among the groups in terms of age, weight or duration of surgery. Postoperative pain was seen in 89% of Group 1 and 77% of Group 2 patients. It was noted in 92% of those in Group 3. These differences were not statistically significant. The back, shoulder and abdomen were the sites most frequently affected. There were no significant differences among the groups in the distribution or intensity of PP. Sore throat was observed in 75% of Group 1 patients and 75% and 100% of those in Groups 2 and 3 respectively. Here again, there were no statistically significant differences among the groups. Analgesics were used by 56% of Group 1 patients postoperatively. They were taken by 23% of Group 2 patients and 75% of Group 3 patients. Only the difference between Groups 2 and 3 was significant ($p < 0.05$). These medications included acetaminophen and non-steroidal anti-inflammatory preparations in most cases.

Discussion: Since its introduction, SDC has been shown to cause a high incidence of PP after many types of surgery especially when no defasciculant was used. Ambulant young females are at high risk for these complications. We contacted our patients on the day after surgery since this time corresponds to the highest incidence of PP when SDC or nondepolarizers (2) are used.

Our results confirm previous investigations (2) showing that outpatient laparoscopy carries a high morbidity. In this study, SDC did not contribute to a higher incidence of PP or sore throat. These findings are at variance with those of Skacel et al. (3) who also compared SDC and ATR for outpatient laparoscopy. However, they did not use a standardized anesthetic technique for both groups. Our findings also disagree with those of Caplan et al. (4) who found a higher incidence of sore throat after SDC in non intubated patients.

SDC has been shown to provide for much better facilitation of endotracheal intubation as compared to ATR and VEC in doses allowable for short procedures. Furthermore, difficulties may arise in reversal of nondepolarizers after short cases. These results show that SDC is an attractive alternative to VEC or ATR for outpatient laparoscopy.

TABLE 1

Group	1 (n=9)	2 (n=13)	3 (n=13)
Relaxant	ATR	VEC	SDC
Postoperative pain[1] %	89	77	92
Sore throat[1] %	75	75	100
Analgesics[1] %	56	23*	75*

[1] on postoperative day 1
* significant difference $p < 0.05$, group 2 vs. 3

REFERENCES

1. Pearce AC, Williams JP, Jones RM. Atracurium for short surgical procedures in day patients. Br J Anaesth 1984;56:973-6.
2. Collins RM, Docherty PW, Plantevin OM. Postoperative morbidity following gynaecological outpatient laparoscopy. A reappraisal of the service. Anaesthesia 1984;39:819-22.
3. Skacel M, Sengupta P, Plantevin OM. Morbidity after day case laparoscopy. A comparison of two techniques of tracheal anaesthesia. Anaesthesia 1986;41:537-41.
4. Caplan LM, Bruce DL, Patel KP, Turndorf H. Succinylcholine-induced postoperative sore throat. Anesth Analg 1983;62:253.

Title: ATRACURIUM AND VECURONIUM DO NOT AFFECT EXTRAOCULAR MUSCLE FUNCTION AFTER OUTPATIENT SURGERY

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Introduction: Postoperative visual disturbances such as double vision may affect up to 71% of patients who have received long acting nondepolarizering muscle relaxants (1). These disturbances may be especially serious for outpatients. In a comparison of atracurium (ATR) and alcuronium, Collins et al. (2) found significantly less postoperative double vision with the former. Extraocular muscle tone (EMT) may be quantitated using the Maddox wing test (3), a simple hand held device. This study was designed to compare EMT after the new shorter acting nondepolarizers ATR and vecuronium (VEC) with succinylcholine (SDC) in outpatients after a standardized anesthetic technique.

Methods: After approval by the Human Subjects Research Committee, 35 ASA Class I or II females undergoing outpatient laparoscopy were selected. All patients received fentanyl 50-150 μg and glycopyrolate 0.2 mg when their IV's were started. After baseline Maddox readings, they were randomly assigned to 3 groups. Following induction with thiopental, Group 1 (n=8) received 0.40 mg/kg ATR; Group 2 (n=14) received 0.08 mg/kg VEC and Group 3 (n=13) received SDC 1 mg/kg followed by a SDC infusion. The patients' eyes were taped during surgery, however nothing was instilled. The investigators were blinded as to the relaxant given. All patients underwent endotracheal intubation. Anesthesia was maintained with isoflurane up to 1.2% inspired in 70% N_2O/30% O_2. Groups 1 and 2 were reversed with neostigmine 0.4 mg/kg and glycopyrolate 0.5 mg after surgery. Starting 30 min after surgery and each 30 min thereafter until discharge, Maddox readings were obtained. Patients requiring eyeglasses used them. Multiple readings were averaged. Patients were contacted on the day after surgery regarding postoperative morbidity by an investigator blinded to the relaxant used. The differences among the groups and the differences within each group as a function of time (repeated measures) were tested by ANOVA followed by Duncan's multiple range test. A $p < 0.05$ was considered significant. The data are presented as mean ± S.D.

Results: The results of the study are summarized in Table 1. There were no statistically significant differences among the groups in terms of age, duration of surgery or weight. All patients were able to sustain 5 sec head lift in the recovery room and all were oriented within 30 min. Maddox readings were highest 30 min after surgery. All had declined to readings which were not significantly different from preop readings by 1.5 hr. There were no statistically significant differences among the groups at any time. No patient complained of diplopia on the day of surgery or on postoperative day 1.

Discussion: Hannington-Kiff (4) noted that patients receiving gallamine had changes in their Maddox readings for 3 hours after surgery even though the relaxant had been reversed. Those receiving SDC had a rapid restoration of these readings. During this postoperative period neither group of his patients was clinically paralyzed. Aromma (5), also using the Maddox test, showed that outpatients receiving alcuronium had changes in EMT after surgery while those who received no nondepolarizers did not.

Our results show that ATR and VEC result in restoration of Maddox readings just as rapidly as SDC. This should enable patients to return to their baseline pre-anesthetic state with any of the relaxants used here without diplopia. These findings are in accord with those of Skacel et al. (6) who found no significant difference in the frequency of diplopia between laparoscopy patients receiving ATR and SDC. The rapid decline in serum levels of ATR and VEC compared to longer acting relaxants such as gallamine or alcuronium is probably responsible for these observations because of the extreme sensitivity of the extra-ocular muscles to relaxants.

Table 1

Group	1(n=8)	2(n=14)	3(n=13)
Relaxant	ATR	VEC	SDC
TIME	MADDOX READINGS*		
Pre-op	2.2 ± 2.0	0.5 ± 4.3	1.9 ± 1.3
Post-op (hrs)			
0.5	10.8 ± 3.9^{a}	8.7 ± 6.3^{b}	12.8 ± 4.5^{c}
1.0	6.6 ± 6.8	5.6 ± 5.4	9.0 ± 5.0^{c}
1.5	4.8 ± 4.3	4.2 ± 5.0	6.5 ± 5.5
2.0	4.9 ± 5.5	3.6 ± 4.5	5.0 ± 4.8
2.5	5.3 ± 5.4	3.0 ± 4.7	4.8 ± 4.6
3.0	5.1 ± 5.7	3.5 ± 3.8	5.6 ± 5.0
3.5	3.6 ± 3.4	3.3 ± 3.9	4.2 ± 4.3
4.0	4.1 ± 2.7	0.5 ± 3.3	4.4 ± 5.3
4.5	5.3 ± 3.1	1.4 ± 3.2	3.1 ± 5.8

*Multiple readings have been averaged. Means ± S.D.
a - different at $p < 0.01$ from its baseline.
b - different at $p < 0.003$ from its baseline.
c - different at $p < 0.001$ from its baseline.

REFERENCES

1. Henegan C, McAuliffe R, Thomas D, Radford P. Morbidity after outpatient anaesthesia. Anaesthesia 1981;36:4-9.
2. Collins KM, Plantevin OM, Doherty PW. Comparison of atracurium and alcuronium in day-case gynaecological surgery. Anaesthesia 1984;39:1130-4.
3. Lyle TK. Practical orthoptics. Philadelphia: Blakiston 1953;127-8.
4. Hannington-Kiff JG. Residual post-operative paralysis. Proc Royal Soc Med 1970;63:73-6.
5. Aromma U. Anaesthesia for short-stay varicose vein surgery. Acta Anaesth Scand 1977;368-73.
6. Skacel M, Sengupta P, Plantevin OM. Morbidity after day case laparoscopy. A comparison of two techniques of tracheal anaesthesia. Anaesthesia 1986;41;537-41.

Title: COMPARISON OF BENZODIAZEPINE PREMEDICATIONS TRIAZOLAM AND DIAZEPAM: AMNESIA, ANXIOLYSIS, AND SEDATION

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INTRODUCTION. Amnesia for unpleasant experiences, reduction of anxiety, and sedation are major aims of premedication.[1] The purpose of this randomized double-blinded placebo controlled study was to compare the anxiolytic, amnestic, and sedative effects of triazolam, a new benzodiazepine, to diazepam.

METHODS. Following Institutional Review Board approval and informed consent, 60 ASA class 1-3 male veterans undergoing intermediate duration surgical procedures were prospectively studied using tests designed to measure physical responsiveness, mental alertness, memory functioning, and reported level of anxiety, preop, immediately prior to anesthetic induction (OR), and postop. Either triazolam 0.5 mg, diazepam 10 mg, or placebo was administered orally 90 minutes preceding OR to three groups of twenty patients. Physical responsiveness was measured by independent observer ratings of wakefulness (sedation) using a modified Stanford Sleepiness Scale and patients' ability to follow directions throughout testing. Mental alertness was assessed by the Finger Tapping Test to measure gross motor speed and the Grooved Pegboard Test to measure fine visual-motor coordination. Short-term memory was evaluated with the Digit Span Subtest of the WAIS-R[2]; long-term memory for events pre-OR was tested with memory cards. Patients' level of anxiety was measured with the State-Trait Anxiety Inventory (STAI).[3] Only those whose initial tests indicated above average anxiety were included in the study. All tests were administered by the same technician. Anesthesia was induced with fentanyl 50-100 mcg, thiamylal 4 mg/kg, and lidocaine 1.5 mg/kg and, following muscle relaxation and intubation, was maintained with isoflurane, nitrous oxide, and oxygen.

RESULTS. Repeated measures analysis of variance (ANOVA) and nonparametric ANOVA methods were used to analyze the data. No significant difference in wakefulness was observed among the three groups two hours prior to OR. Following drug administration, triazolam and diazepam produced significant sedation compared to placebo controls ($p < .01$) at OR and in the recovery room (Figure 1). Although the triazolam group experienced some difficulty moving themselves from the gurney to the operating table, no difference in following directions during testing was observed. No significant difference in finger tapping was observed among the three groups at any measurement time. However, patients in the triazolam group required significantly more time to complete the grooved pegboard task ($p < .05$) than the other two groups at OR. Mean digit span scores were significantly depressed in the triazolam group compared to the other two groups ($p < .01$) at OR but no differences between the groups were observed 24 hours pre or postop (Figure 2). In the memory card test, only 27.3% of the triazolam group could recall a stimulus word compared to 80% of the diazepam group and 100% of the placebo group 24 hours postop. In the triazolam group 44% were able to recall a figure stimulus versus 90% in the diazepam group and 100% in the placebo group at that time. No differences among the three groups' mean anxiety levels at each measurement point were observed. However, when each patient was used as his own control, a significant reduction in anxiety level occurred in both the triazolam ($p < .05$) and diazepam groups ($p<.01$) from 24 hours preop to OR but not in the placebo group.

DISCUSSION. The authors concluded that triazolam was a useful oral premedication since it provided comparable levels of anxiolysis and sedation, as well as, greater amnesia of events during the immediate perioperative period when compared to the effects of diazepam.

REFERENCES.

1. Dundee, J.W., Moore, J., Nicholl, R.M. Studies of drugs given before anaesthesia I: A method of preoperative assessment. Br J Anaesth 1962; 34:458-62.
2. Spielberger, C.D., Gorsuch, R.L., Lushene, R. Manual for the State-Trait Anxiety Inventory. Palo Alto: Consulting Psychologists Press, 1969.
3. Wechsler, D. WAIS-R manual. New York: The Psychological Corp., 1981.

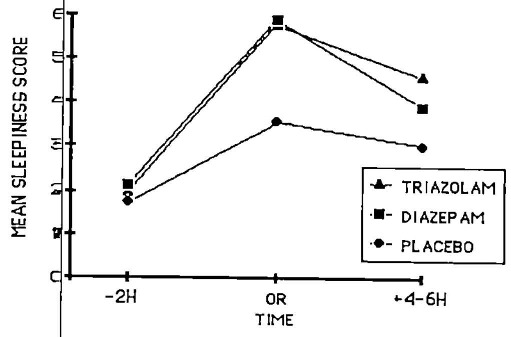

FIGURE 1: WAKEFULNESS

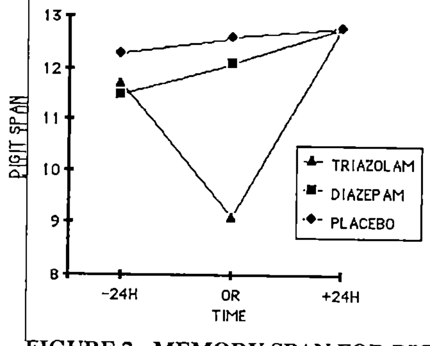

FIGURE 2: MEMORY SPAN FOR DIGITS

Title: CALCIUM CHANNEL BLOCKERS AND CALCIUM ADMINISTRATION DURING WEANING FROM CARDIOPULMONARY BYPASS

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Introduction. Calcium channel blocking drugs (CaChB) are frequently used in the treatment of patients with angina pectoris. Many of these patients present to surgery for coronary artery bypass grafting (CABG). Calcium chloride ($CaCl_2$) is routinely administered during surgery shortly before weaning from cardiopulmonary bypass (CPB). However, objective data concerning plasma calcium levels (Ca^{++}) and dose requirement of $CaCl_2$ during this period are lacking. Moreover, the influence of the presence of CaChB on the intraoperative management of these parameters is unclear. This study was undertaken to determine if CABG patients on CaChB were managed differently with respect to $CaCl_2$ administration than patients not on these drugs, and what effect this may have had on the process of weaning from CPB.

Materials and Methods. Records of patients who underwent CABG at our institution during 1985 were reviewed. 38 patients with the following preoperative profile were selected: 1) no recent history of congestive heart failure or inotrope administration, 2) left ventricular ejection fraction $\geq$ 40% by MUGA scan, echocardiography, or left ventricular cineangiography. These patients were then grouped according to the presence and/or time of administration of CaChB prior to CABG surgery. Non-CaBlk patients (n=18) had not received CaChB within 24 hours of surgery, while CaBlk patients (n=20) were on CaChB (diltiazem 30-90 mg. PO Q6h or nifedipine 20-30 mg. PO Q8h) and had received their usual dose on the morning of surgery. Data collected for comparison between groups included: patient age, severity of coronary artery disease, clinical classification of angina, anti-anginal therapy other than CaChB (nitrates, beta blockers, intra-aortic balloon pump (IABP)), duration of CPB and aortic cross-clamping (AoX), $CaCl_2$ dose given prior to weaning from CPB ($CaCl_2$CPB) and within 30 minutes afterwards ($CaCl_2$post), Ca^{++} (measured either as the ionized fraction (Ca^{++}i) or as the total plasma level (Ca^{++}T)) both before the $CaCl_2$CPB dose and immediately after CPB weaning. Student's T-test for unpaired data or analysis of covariance was applied where appropriate. Comparisons were considered significantly different at the $p < 0.05$ level.

Results. The mean age of patients in each group was similar: Non-CaBlk, 62.0 years (range 39-77), CaBlk, 64.3 years (range 56-75). 15 patients in each group had significant left main or severe three vessel coronary artery disease. 72% of the Non-CaBlk patients and 75% of the CaBlk patients were classified as having unstable angina. All patients had similar induction and management of general anesthesia: high dose narcotics (fentanyl or sufentanil), muscle relaxants, and supplemental isoflurane. All patients were hemodynamically stable during the induction period and prior to institution of CPB. Routine non-pulsatile CPB, hypothermia (20-25° C.), and cold potassium cardioplegia during AoX were utilized. Tables 1 - 5 summarize several categories of data collected. Between patient groups, there was no significant difference in other anti-anginal therapy, durations of CPB or AoX, $CaCl_2$ dose either pre- or post-CPB, or Ca^{++} levels pre- or post-CPB. Interestingly, 78% of Non-CaBlk patients and 70% of CaBlk patients were hypercalemic immediately post-CPB, whether measured as Ca^{++}i or Ca^{++}T. A similar number of patients in each group received inotropic support post-CPB. One patient from each group failed the initial attempt to wean from CPB and required institution of IABP. One intraoperative death occurred in the Non-CaBlk group only.

Discussion. The parameters examined in this study are among the possible predictors of the success of weaning from CPB. These variables proved to be strikingly similar between patient groups. Our findings that no additional $CaCl_2$ was given to the patients on CaChB and that this group had the same success in being removed from CPB as the Non-CaBlk group suggest that special consideration or planning for calcium administration in CaBlk patients is unnecessary. Moreover, the fact that hypercalcemia was noted in a majority of patients in both groups in the immediate post-CPB period and the potential hazards of calcium in reperfused myocardium would suggest caution in administering $CaCl_2$ during this period.

Table 1. Other Anti-anginal Therapy (% of patients)

	Nitrates	Beta-Blockers	IABP
Non-CaBlk	100	94	11
CaBlk	100	90	10

Table 2. CPB and AoX Times (minutes, mean±SEM)

	CPB	AoX
Non-CaBlk	141±13	65±4
CaBlk	127±7	66±4

Table 3. $CaCl_2$ Administration (grams, mean±SEM)

	$CaCl_2$CPB	$CaCl_2$post	Total
Non-CaBlk	2.7±0.2	0.8±0.2	3.5±0.3
CaBlk	2.9±0.2	0.8±0.2	3.6±0.3

Table 4. Ca^{++}i/Ca^{++}T Levels (mean±SEM)
(mmol/L Ca^{++}i, normal 1.1-1.3)
(mg/dL Ca^{++}T, normal 8.8-10.4)

		Pre $CaCl_2$CPB	Post CPB
Non-CaBlk	Ca^{++}i,(n=10)	1.08±0.02	1.45±0.07
	Ca^{++}T,(n=8)	6.9±0.3	12.3±0.1
CaBlk	Ca^{++}i,(n=10)	1.10±0.03	1.62±0.10
	Ca^{++}T,(n=10)	7.2±0.3	11.4±0.4

Table 5. Support during CPB Weaning (% of patients)

	Inotropes	Intraoperative IABP
Non-CaBlk	61	6
CaBlk	55	5

Title: ACCELERATED RECOVERY FROM COMBINED ATRACURIUM-VECURONIUM NEUROMUSCULAR BLOCKADE IN MAN

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Introduction. Combinations of nondepolarizing muscle relaxants have been employed in numerous laboratory and clinical studies. One reported advantage is more rapid recovery from the same degree of block in patients given potentiating relaxant combinations than those given a single relaxant (1,2). This study prospectively investigated this phenomenon in patients given a combination of atracurium and vecuronium.

Methods and Materials. The study protocol was approved by the institution's Human Investigation Committee, and written informed consent was obtained from all patients. The subjects were 30 adult patients, ASA physical status 1 or 2. No premedication was given. Anesthesia was induced with thiopental 4-6 mg/kg IV and maintained with fentanyl 3-5 μg/kg IV and N_2O, 67% in O_2. Neuromuscular blockade was monitored with a force transducer which measured adductor pollicus twitch tension in response to supramaximal ulnar nerve stimulation at 0.15 Hz delivered for 0.15 ms via 25-gauge needles placed subcutaneously. Patients were allocated randomly by lot (10 patients/ group) to receive either atracurium (0.5 mg/kg), vecuronium (0.1 mg/kg), or atracurium (0.125 mg/kg) followed immediately by vecuronium (0.025 mg/kg). Times to initial twitch depression and to maximum twitch depression, as well as the magnitude of neuromuscular block produced, were measured, as were times to 10, 25, 50, 75, and 90% recovery of initial twitch height. Statistical analysis was performed using one-way analysis of variance (ANOVA); groups which differed significantly by ANOVA were tested with two-tailed t-tests (Bonferroni correction) to determine differences between groups, with $p<0.05$ considered significant.

Results. Mean ages and weights did not differ significantly between the three groups. All patients had 100% neuromuscular block, and times to initial and maximal twitch height depression did not differ significantly between any of the groups. Profiles of twitch height recovery are shown in the table. Recovery to 10, 25, 50, and 90% of control twitch height was significantly faster in the group receiving the atracurium/vecuronium combination than in either of the other two groups.

Discussion. Two studies employing combinations of nondepolarizing relaxants--pancuronium/metocurine (1) or pancuronium/d-tubocurarine (2)--demonstrated no significant differences in onset time or maximum block between patients receiving single or combined relaxants. However, the smaller individual relaxant doses in patients receiving relaxant combinations were associated with less hemodynamic change. These studies demonstrated that time to 25% recovery of twitch height was significantly shorter in groups receiving combinations than in those receiving a single relaxant (1,2). The results of the present study extend these observations to the combination of atracurium and vecuronium. Relevant clinically, as well as statistically significant, was the notably faster recovery of twitch tension in the group receiving combined atracurium and vecuronium (Table). Thus, neuromuscular block in patients receiving a combined atracurium/vecuronium reginen was readily reversible (i.e., spontaneous recovery to 10 of control twitch height) 10-15 min earlier than in patients receiving an intubating dose of either atracurium or vecuronium alone. Similarly, spontaneous recovery to 90% of control twitch height occurred almost 20 minutes faster, approximately 33% more rapidly, in the group receiving the atracurium/vecuronium combination than in either group receiving a single relaxant. The markedly shortened recovery time observed with the combination of atracurium and vecuronium may be of value in situations where a brief duration of profound relaxation is required, for instance, for short surgical procedures or in the outpatient setting.

Table. Recovery following atracurium (atr.) 0.5 mg/kg, vecuronium (vec.) 0.1 mg/kg, or atracurium 0.125 mg/kg + vecuronium 0.025 mg/kg.

Relaxant and dose (mg/kg)	Time(min) to % recovery from neuromuscular block				
	10%	25%	50%	75%	90%
Atracurium 0.5	42±2	48±2	54±2	60±2	66±2
Vecuronium 0.1	38±2	43±2	50±3	58±4	66±4
Atr. 0.125 + Vec. 0.025	27±1*	32±1*	38±2*	43±2†	48±2*

Values are mean ± SEM
*p<0.0 vs. atracurium 0.5 mg/kg and vecuronium 0.1 mg/kg groups
†p<0.0 vs. atracurium 0.5 mg/kg group

References.

1. Lebowitz PW, Ramsey FM, Savarese JJ, Ali HH, and deBros FM. Combination of pancuronium and metocurine: neuromuscular and hemodynamic advantages over pancuronium alone. Anesth Analg 1981; 60:12.

2. Mirakhur RK, Pandit SK, Ferres CJ, and Gibson FM. Time course of muscle relaxation with a combination of pancuronium and d-tubocurarine. Anesth Analg 1984; 63:437.

Title: EFFECT OF PREMEDICATION ON OXYGEN SATURATION IN CHILDREN WITH CYANOTIC
CONGENITAL HEART DISEASE

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Introduction: Optimal anesthetic management of children with cyanotic congenital heart disease (CCHD) should minimize decreases in arterial oxygen saturation (SaO_2). Preoxygenation and induction of anesthesia with 100% oxygen have been shown to have a beneficial effect on SaO_2 in these children.[1] However, the effect of premedication on SaO_2 in children with CCHD has not been studied. Therefore, we investigated the effect of premedication on SaO_2 in children with cyanotic congenital heart disease.

Methods: Following ethical committee approval, seven children with CCHD presenting for elective cardiac surgery were studied. Each child was his/her own control and was studied during two 90 minute periods: 1) control - commencing 25½ hours prior to surgery (day 1); 2) study - commencing 1½ hours prior to surgery (day 2). On day 2, each child was premedicated with pentobarbitone 2 mg/kg orally or rectally 90 minutes preoperatively (time 0), and morphine 0.2 mg/kg and atropine 0.02 mg/kg intramuscularly 60 minutes preoperatively (time 30 minutes). SaO_2 and heart rate (HR) were continuously recorded during each period using a pulse oximeter sensor (Nellcor Pulse Oximeter) firmly attached to the great toe. SaO_2 and HR data were analyzed at 3 minute intervals during each period. The mean values for each patient on days 1 and 2 were compared using the Student's paired t-test. The mean values for all patients at times 0, 30, 60, and 90 minutes after the preoperative pentobarbitone on days 1 and 2 were compared at each of the four times using the Student's unpaired t-test. Statistical significance was accepted as $p < 0.05$.

Results: The mean (±SEM) age and weight for the seven children were 64.6 (±5.4) months and 18.2 (±1.5) kg respectively. All patients were cyanotic with a mean (±SEM) hemoglobin concentration of 173 (±8.6) g/litre. The indications for surgery included repair of tetralogy of Fallot (5 patients), Mustard repair for transposition of great arteries together with repair of VSD (1) and Fontan procedure for univentricular heart (1). The mean values of SaO_2 for each child on days 1 and 2 (Table 1) did not differ significantly. However, there were significant changes in HR in 4 children on day 2. The mean values of SaO_2 and HR for all 7 children at the four times on days 1 and 2 (Table 2) differed significantly only at the 30 minute measurements. The mean (±SEM) duration of the desaturation at 30 minutes on day 2 was 2.7 (±0.9) minutes.

Discussion: We have shown that premedication in children with CCHD does not cause a progressive decrease in SaO_2 with time. However, SaO_2 does decrease significantly, albeit transiently, following an intramuscular injection (Table 2). This desaturation is associated with a period of crying and/or struggling. The significant changes in heart rate do not directly correlate with the changes in arterial oxygen saturation. The results of this study sugest that either supplemental oxygen should be used to attenuate the desaturation after parenteral injections or that oral and rectal premedication may be preferable to parenteral medication in these children.

References:

1. Laishley RS, Kline C, Burrows FA, Lerman J, Roy WL. Effect on oxygen saturation by different anesthetic induction agents in cyanotic congenital heart disease. Anesthesiology 1985; A456

TABLE 1

Patient	SaO_2 (%) Day 1	SaO_2 (%) Day 2	Heart rate Day 1	Heart rate Day 2
1	85.8	85.8	104.5	108.0
	±0.3	±0.4	±1.6	±1.8
2	85.7	85.8	128.1	140.4**
	±0.4	±0.8	±1.7	±3.2
3	84.4	85.1	122.9	112.4**
	±0.2	±0.5	±0.7	±1.7
4	81.0	80.3	129.3	104.0**
	±0.2	±0.5	±0.9	±2.1
5	79.8	78.7	98.3	93.9
	±0.5	±0.8	±1.7	±2.6
6	83.0	80.7	103.3	107.0
	±0.5	±1.2	±1.6	±5.4
7	85.8	85.4	93.4	102.8*
	±1.0	±0.9	±2.4	±2.4

Data are mean ± SEM; * $p < 0.01$;
** $p < 0.001$ different from day 1.

TABLE 2

Time (mins)	SaO_2 (%) Day 1	SaO_2 (%) Day 2	Heart rate Day 1	Heart rate Day 2
0	84.9	84.3	105.9	104.9
	±0.9	±1.4	±7.5	±4.4
30	84.0	71.6**	112.3	143.6*
	±1.1	±1.9	±6.9	±9.0
60	82.9	83.4	113.9	125.6
	±0.9	±1.2	±6.6	±7.6
90	83.0	83.3	112.3	119.6
	±1.0	±1.6	±5.8	±4.1

Data are mean ± SEM; * $p < 0.05$;
** $p < 0.001$ different from day 1.

Title: ANTERIOR FONTANEL PRESSURE RESPONSE TO ENDOTRACHEAL INTUBATION IN NEONATES AND YOUNG INFANTS

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Introduction: Intracranial hemorrhage may develop following awake intubation in the premature infant or neonate with a history of birth asphyxia. Awake intubation is often indicated in these infants for both anatomical and physiological reasons. In order to compare the effects of awake intubation with intubation during general anesthesia, we measured the anterior fontanel pressure (AFP) in two groups of infants.

Methods: With approval from our Human Research Committee, informed parental consent was obtained. Twenty-four patients, ASA I or II, fasting, unpremedicated, and scheduled for elective general surgery were studied. Patients with neurological disease were excluded from the study. On arrival in the operating room, all patients were placed supine and the hair over the anterior fontanel shaved. After calibration, a Ladd transducer[1] was placed over the fontanel and secured in place by a 3cm x 3cm piece of 'Reston' foam, to minimize the effects of application pressure. All patients were preoxygenated for two minutes. Patients in Group I (awake intubation) received atropine 0.02 mg/kg intravenously 2 minutes before awake intubation was performed. Anesthesia was then induced with halothane or isoflurane in oxygen, and supplemented with nitrous oxide. Patients in Group II (general anesthesia) were anesthetized with sodium thiopentone 5 mg/kg, atropine 0.02 mg/kg and suxamethonium 2 mg/kg intravenously. After a brief period of manual ventilation with 100% oxygen, the trachea was intubated. Anesthesia was maintained with halothane or isoflurane in oxygen, supplemented with nitrous oxide. AFP was recorded at five intervals: quiet, crying, laryngoscopy, immediately post-intubation, and during maintenance anesthesia (GA). Statistical significance ($p < 0.05$) was determined by comparing values within groups with quiet measurements using 2-way analysis of variance, and by comparing values between groups at the five intervals using Student's unpaired t-test.

Results: The demographic data for Group I (n=14) and Group II (n=10) differed significantly in age and weight (Table). There was no significant difference in gestational age between groups. AFP increased significantly from quiet values with crying in both groups. In group I AFP increased significantly at laryngoscopy and immediately following intubation when compared to quiet values. AFP during laryngoscopy in Group I did not change significantly when compared to values during crying (Figure). In contrast, in Group II, AFP was significantly lower at laryngoscopy and intubation than during crying. The maximum values for AFP during laryngoscopy and intubation in both groups were of shorter duration than during crying.

Discussion: We have demonstrated highly significant increases in AFP in neonates and young infants undergoing awake endotracheal intubation. The magnitude of these increases was significantly less in infants anesthetized prior to intubation. Significant increases in AFP above quiet values were also seen in the crying infant. These results imply an increase in intracranial pressure due to an increase in venous pressure and/or in mean arterial blood pressure. This may predispose susceptible neonates and young infants to intracranial hemorrhage. However, our results also suggest that the short, but highly significant increase in AFP during awake intubation may be of less importance than has been previously assumed, when compared to the prolonged increases seen during crying or struggling in the healthy neonate or young infant. Further studies are indicated to identify and attenuate these cardiovascular responses to awake intubation.

References:

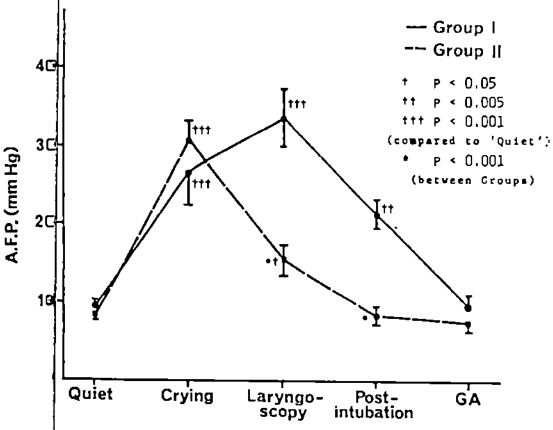
1. Vidyasagar D, Raju TNK: A simple non-invasive technique of measuring intracranial pressure in the newborn. Pediatrics 59:957, 1977

TABLE

	Group I	Group II
Age (days)	19.3 ± 2.8	34.1 ± 5.2*
Weight (kg)	3.2 ± 0.2	3.9 ± 0.2*
Gestational age (wks)	38.1 ± 0.7	38.4 ± 0.8

$p < 0.05$; Data are mean ± S.E.M.

FIGURE



Title: **ORAL TRANSMUCOSAL FENTANYL PREMEDICATION IN CHILDREN**

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Introduction. Fentanyl rapidly passes through oral mucosal membranes when incorporated in a candy matrix and results in sedation, analgesia and, in sufficient doses, respiratory depression in adult volunteers. Although initial studies suggested that oral transmucosal fentanyl citrate (OTFC) in the form of a fentanyl lollipop might be an ideal form of premedication in children, ideal dose ranges were unknown and no experience was available in this population. Thus the objectives of this investigation were to determine the acceptability of fentanyl lollipop premedication and the ideal dose range(s) in children about to undergo general anesthesia and operation.

Methods. Approval was received from the FDA and the human institutional research board and permission obtained from the parents of 47 children aged 2 to 13 about to undergo ENT, ophthalmologic, urologic or orthopedic operations. The lollipops were made by heating a candy base and adding 100, 200, 300, 400, 500, 700 or 1000 ug of fentanyl citrate crystals. Following this, the candy-fentanyl mixture was poured into molds, a stick added and the lollipops allowed to cool and harden before removal from the molds

The children were divided into four groups (I-IV) with respect to the dose of fentanyl they received in the lollipop; Group I = 5-10; group II = 10-15, group III = 15-20 and group IV = 20-25 ug/kg. Each child had a standard pediatric blood pressure cuff placed on an upper arm and a Nelcor pulse oximeter on a finger or toe. Oxygen saturation was continuously observed throughout the study and recorded along with blood pressure, heart and respiratory rates (via radial artery and chest palpations) every 15 min in the preoperative holding area and 5 min during anesthesic induction, though-out operation and in the recovery room. The children were also graded in the holding area and during induction as to the effectiveness (sedation index) of the premedication (scale of 5 - aware and alert to 1 - asleep, no response to questions). Similar evaluations were made with respect to the presence or absence of fear, the child's ability to cooperate, the quality of the anesthetic induction and emergence, times to awaken, become verbally communicative and oriented and the incidence of nausea, vomiting and pruritus. All patients had anesthesia induced and maintained with halothane, N_2O and oxygen.

Results. Three of the 47 children were eliminated from evaluation because they refused to take the lollipop or did not have sufficient time to finish it before being called to the operating room. Forty-three of the 44 children studied were fully cooperative and visably enjoyed the pre-medication experience. Onset of sedation was rapid, from 5-20 minutes and heralded by an itchy nose or eye in 17 of 20 patients in groups I and II and in all patients in groups III and IV. Sedation scores after the lollipop and prior to induction were dose related and times for mean peak effect ranged from 25 to 45 min. Induction was graded good or excellent in 37 of the 44 children but no statistical difference was noted between the groups. Recovery room emergence was rated excellent in 29 of the 44 patients with no group being significantly better than another. However, group III patients were awake, verbally communicative and oriented sooner than patients in the other three groups. In patients in Group III orientation was achieved an average of 11 min sooner than group II and 18 and 25 min sooner than groups I and IV, respectively. Times of discharge from the recovery room were similar in the four groups and averaged 71 to 78 mins. Three patients became nauseated and/or vomited pre-operatively. In the recovery room, 11 patients experienced nausea and/or vomiting, 4 of the 11 were in Group IV. Four children of 12 in group IV were the only ones to experience a transient episode in which O_2 saturation was $< 90\%$ at any time during the study. These isolated episodes all occurred prior to anesthetic induction and responded to commands to breathe.

Discussion. The results this study demonstrate that the fentanyl lollipop is an effective and safe method of premedicating children and that the ideal dosage range in terms of optimizing sedation and minimizing side effects is 15-20 ug/kg.

Title: THE RESPIRATORY EFFECTS OF PROPOFOL WITH AND WITHOUT FENTANYL

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Introduction. Propofol, a new alkyphenol anesthetic induction agent has been proposed as an alternative to thiopental because of its rapid elimination phase ($T_{1/2}B$ = 55 min). Accordingly, recovery from anesthesia should be faster and residual respiratory depression less than with thiopental. The purpose of this study was to compare the acute and residual respiratory effects of Propofol (P) to Thiopental (T). Because analgesic compounds are frequently used during anesthetic induction, comparison included patients with or without Fentanyl (F) pretreatment.

Methods. Approval was received from the human institutional review board and informed consent obtained from 80 Class I-II patients, 18-65 years old, scheduled for orthopedic or gynecologic surgery. Patients satisfying the entry criteria were randomized into four groups. Half received F, 3.5 ug/kg, 5 min prior to an induction dose of either P, 2.5 mg/kg, or T, 4 mg/kg. The other half received a placebo (saline) injection prior to either P or T. All patients received diazepam, 0.15 mg/kg, po, 60-90 min prior to induction of anesthesia. Prior to surgery, resting $P_{ET}CO_2$ was measured (Beckman LB-2 infrared CO2 analyzer) and baseline respiratory drive data ($V_E/P_{ET}CO_2$, and $P_{0.1}/P_{ET}CO_2$) were obtained by a modified Read method of CO_2 rebreathing. After an intravenous infusion was begun, the patients were taken to the OR where an EKG was started and an automatic BP cuff placed on an upper arm. A Bourns spirometer was inserted in the anesthesia breathing circuit and preinduction respiratory rate (RR) and tidal volume (TV) were obtained by having the patient breathe through an occlusive face mask for 3 min. Following this, patients were given F or placebo (saline) and after 5 more min had anesthesia induced with either T or D. RR and TV were recorded every min after F or placebo (for 5 min) and then every 15 sec from the start of induction until apnea occurred. Heart rate (HR) and systolic (SBP) and diastolic (DBP) blood pressures were recorded every min from the administration of the pretreatment medication until 3 min following induction. Induction time, the time from administration of P or T until loss of the eye-lid reflex was noted. Three min following induction, the patient was paralyzed with Succinylcholine and intubated. General anesthesia was maintained with Isoflurane (0.5-1.5%) and 60% N_2O in O_2. Recovery was evaluated by measuring times to awakening and orientation following discontinuation of all inhalation agents. Side effects including myoclonus, pain on injection, rigidity and nausea and vomiting were noted during induction and in the recovery room. Sixty min after patients arrived in the recovery room respiratory function was re-evaluated utilizing CO_2 rebreathing. Data was analyzed for statistical significance using Wilcoxon, Kruskal-Wallis, Chi-square and analysis of variance tests.

Results. Demographic data of the four groups were similar as were induction times of patients receiving P (45.1 ± 14.5 sec) or T (42.8 ± 13.3) alone. When F was given prior to P or T, induction times significantly decreased ($P < 0.001$) to 32.8 ± 9.3 and 29.6 ± 10.2 sec, respectively. RR increased during the first 30 sec of induction and then decreased dramatically until apnea occurred (in 45 sec) in patients receiving P or T alone. After F pretreatment, all patients had rapid decreases in RR progressing to apnea in 30. TV increased early after T alone (first 30 sec) and then decreased thereafter. In contrast, TV rapidly decreased after P alone and in all patients getting F and then P or T.

Postoperative resting $P_{ET}CO_2$, $V_E/P_{ET}CO_2$ and $P_{0.1}/P_{ET}CO_2$ were similar to preop values in both groups not receiving fentanyl. In contrast, both groups getting F pretreatment experienced marked decreases in $V_E/P_{ET}CO_2$ (30-60%) after 60 min in the recovery room. Interestingly, resting $P_{ET}CO_2$ were not significantly changed from baseline values.

Without F, both P and T resulted in small decreases (5-10%) in SBP and DBP. Fentanyl pretreatment caused significaly greater decreases in SBP and DBP, particularly after P (-27% vs -15% after T). Both induction agents increased HR (P = 12%; T = 21%). These increases were blunted but not eliminated when patients were pretreated with F.

Recovery time was similar in all four groups irrespective of F pretreatment. While there was no difference between groups in the incidence of nausea and vomiting, pain on injection was seen more frequently with P (60%) than T (10%) and myoclonus occurred only after P (35%). Although overall the incidence of side effects were decreased with F pretreatment, the frequency with P plus F (65%) was still greater than T plus F (45%).

Discussion. The results of this study demonstrate that P and T cause respiratory depression of similar degree and duration which is of little consequence after surgery. The data also indicate that pretreatment with 3.5 ug/kg of fentanyl before P or T hastens anesthetic induction but causes more impressive decreases in arterial blood pressure (particularly after D) and results in significant residual postoperative respiratory depression. Finally, our findings suggest that Propofol provides no advantages and is associated with more side effects than Thiopental.

Title: TOXICITY OF SEVOFLURANE IN RATS

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Introduction. Sevoflurane is a potent inhaled anesthetic (1,2) whose rapid uptake and elimination are due to a low blood/gas partition coefficient. To be clinically useful, sevoflurane must demonstrate no toxicity. Sevoflurane is unstable in soda lime (1) and therefore is potentially toxic.

Renal and hepatic damage have been found after administration of sevoflurane in the presence of soda lime, but this damage was attributed to hyperthermia and a thermoregulatory defect rather than a specific chemical toxicity (3). Other studies did not find hepatic injury after sevoflurane given with soda lime (1,2). However, in addition to products of biodegradation or breakdown by soda lime, injury may require an increase in hepatic O_2 consumption (hyperthermia, phenobarbital pretreatment) and/or a decrease in O_2 availability (hypoxia, decreased hepatic blood flow consequent to anesthetic administration).

In the present study, we address three questions: 1) is sevoflurane toxic when administered in the presence of soda lime; 2) does hypoxia exaggerate this toxicity; and 3) is sevoflurane more toxic than isoflurane or halothane?

Methods. After approval from our Committee on Animal Research, we obtained 2-3 months old, male, specific pathogen free, Sprague-Dawley rats weighing 250g to 350g. To induce hepatic enzymes, the rats were pretreated for five days by adding phenobarbital, 1 mg/ml, to their drinking water. Rats consuming less than 50 mg phenobarbital per 5 day period were discarded. Phenobarbital was discontinued for 24 hours prior to anesthetic exposure.

Each rat was placed in an individual exposure chamber and received anesthetic (except for control rats) at 0.9 to 1 MAC for four hours in a background gas containing 12%, 14%, or 100% O_2. Rectal temperatures of each rat were measured (except for control rats in the 14% O_2 groups) and the average temperature maintained between 38°C and 39°C.

Anesthetic was administered from temperature compensated vaporizers. The gases directed through the vaporizer consisted of O_2 and 4% CO_2, balance N_2, to produce an inspired concentration of O_2 without CO_2 of 12%, 14%, or 100%. The gases plus anesthetic were directed through a humidifying canister and then through four standard soda lime absorbers maintained at 54°C. Gas concentrations in the effluent from the absorbers were monitored by infrared analysis and gas chromatography to ensure that 0.9 to 1 MAC concentrations were sustained and that no CO_2 was delivered to the rats. At the end of the four hour exposure period, the anesthetic was discontinued and the rats given air to breathe.

One day later, the rats were killed by inhalation of CO_2. Duodenum, kidney, liver, and pancreas were removed, and a slide for microscopy prepared from each specimen. The randomized slides were examined by a pathologist (LDF) who was not aware of the treatment given each rat. Each slide of liver was assessed for the percentage of the lobule that showed swelling but not necrosis and for the percentage that showed necrosis. The sum of these two grades of injury equalled the percentage of the entire lobule that was injured. Our data were analyzed with an analysis of variance, Fisher's exact test, and chi squared analysis.

Results. Sevoflurane did not differ from isoflurane in the extent of hepatic injury produced at each concentration of O_2 (Table). Hepatic injury was greater in rats given halothane and less in control rats. At 100% O_2, no rat demonstrated hepatic injury. The passage of sevoflurane through soda lime did not influence the extent of hepatic injury at either 14% or 100% O_2. Injury to duodenum, pancreas, and kidney was minimal and did not differ among the groups.

Discussion. Hepatic injury from sevoflurane was inversely proportional to the administered O_2 concentration. Sevoflurane and isoflurane were indistinguishable in the degree of hepatic injury they produced. This similarity implies that sevoflurane is no more toxic than isoflurane, currently the most widely used potent inhaled anesthetic. Finally, degradation of sevoflurane by soda lime did not increase toxicity.

References.

1. Wallin RF, Regan BM, Napoli MD, Stern IJ. Sevoflurane: A new inhalational anesthetic agent. Anesth Analg 54:758-765, 1975.

2. Holaday DA, Smith FR. Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. Anesthesiology 54:100-106, 1981.

3. Hitt BA, Mazze RI, Cook TL, Beppu WJ, Kosek JC. Thermoregulatory defect in rats during anesthesia. Anesth Analg 56:9-14, 1977.

HEPATIC INJURY ASSOCIATED WITH HYPOXIA, ANESTHETIC, AND USE OF SODA LIME.

				# OF RATS WITH INJURY		% OF LOBULE INJURED		% OF LOBULE NECROSED	
Agent	O_2%	Soda	n	Ratio	%	Mean	S.D.	Mean	S.D.
Ctl	12	yes	22	13/22	57.1	11.3	18.8	4.9	12.8
Halo	12	yes	27	27/27	100.0*	30.6	12.8*	13.3	13.9
Iso	12	yes	26	23/26	88.5*	23.9	19.4*	13.1	15.5
Sevo	12	yes	38	33/38	86.8*	21.5	13.7†	9.2	8.5
Ctl	14	yes	38	4/38	10.5	0.8	2.8	0.1	0.2
Halo	14	yes	23	22/23	95.7*	20.7	18.4*	10.2	11.5*
Iso	14	yes	14	8/14	57.1*	3.8	6.3†	0.9	1.9†
Sevo	14	yes	26	11/26	42.3*†	6.5	11.6†	2.7	5.3†
Sevo	14	no	12	6/12	50.0*†	6.7	12.4†	3.6	8.6
Ctl	100	yes	25	0/25	0.0	0.0	0.0	0.0	0.0
Sevo	100	yes	26	0/26	0.0	0.0	0.0	0.0	0.0
Sevo	100	no	13	0/13	0.0	0.0	0.0	0.0	0.0

*Differs ($P < 0.05$ with Bonferroni correction) from control. †Differs ($P < 0.05$) from halothane.

TITLE: THE EFFECT OF PRETREATMENT WITH CURARE ON NEUROMUSCULAR TRANSMISSION

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Introduction: "It was the most unpleasant experience of my life" - a member of the anesthetic staff describing the effects of curare (dTC) 3 mg, given before induction of anesthesia. Patients are known to vary markedly in their response to dTC. dTC 0.1 mg/kg will cause complete neuromuscular blockade in 7% of patients.[1] Since dTC 3 mg (approximately 0.05 mg/kg) is routinely used before induction of anesthesia to eliminate suxamethonium induced fasiculations, we studied the effects of this dose of dTC on neuromuscular function, to determine what proportion of patients exhibit an exaggerated response.

Method: The effects of dTC were monitored in 62 unselected adult patients, either unpremedicated or premedicated with diazepam, scheduled for elective surgery. Neuromuscular transmission was monitored using a Neuromuscular Transmission monitor (Puritan-Bennett). This device contains a peripheral nerve stimulator, compound emg analyser and will deliver a supramaximal "train of four" every 20 sec and, following calibration, will display T1 as a percentage of baseline T1 and the T1/T4 ratio. Stimulation electrodes were placed over the ulnar nerve, recording electrodes over the hypothenar eminence and a palmar reference was used. Since supramaximal stimulation is painful when awake, calibration was carried out following a sleep dose of thiopental. Following baseline measurements, curare 0.05 mg/kg was administered as a bolus and neuromuscular transmission monitored for 5 min. During this time the patients breathed (or ventilation was assisted) with N_2O/O_2 (F_IO_2 = 0.3) and further thiopental given as clinically indicated.

Results: By 5 minutes 25 patients (40%) had less 10% reduction in neuromuscular transmission (T1 versus pre-dTC T1) but 16 patients (25%) had more than 20% reduction. One patient had a 42% reduction (Figure 1). The distribution of T1 reduction at 5 minutes in our sample is shown in Figure 2. There was no evidence of fade (judged by a reduction in T1/T4 ratio) in our sample nor did age, sex, race or previous medication appear to influence degree of block.

Discussion: This variation in response to dTC confirms earlier observations obtained using double the dose of dTC.[1] However, the marked degree of blockade obtained in 25 % of our sample using only 0.05 mg/kg of dTC is surprising. It is likely that, had these patients been awake, they would have been symptomatic. For this reason, we recommend that if pretreatment with a non-depolarizing muscle relaxant is used before suxamethonium, it is administered after induction of anesthesia.

Reference: 1. Katz RL. Muscle Relaxants Excerpta Med., NY, p. 321, 1975.

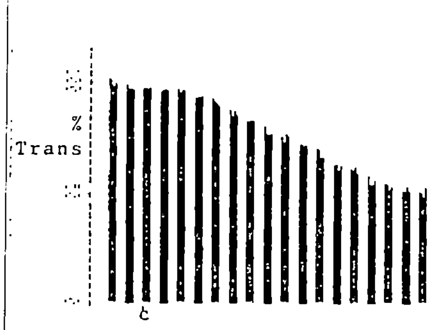

Figure 1. Recording from one subject. dTC was given at the mark c, by 5 min there was a 42% reduction in neuromuscular transmission.

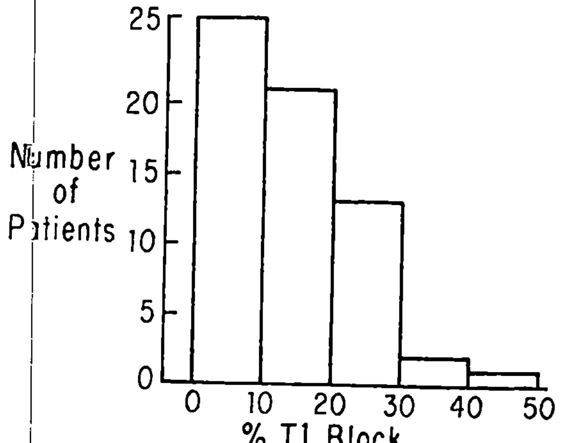

Figure 2. Histogram showing the reduction in T1 at 5 min after dTC, expressed as a percentage of the control value.

Title: IMPORTANCE OF MAINTAINING CONSTANT (EUTHERMIC) VENTILATION DURING HYPOTHERMIC CARDIOPULMONARY BYPASS

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Introduction. It is generally agreed that at normal body temperature (t°) ideal values of arterial pH and PCO_2 are 7.40 and 40 mmHg, respectively.(1) However, normal values for a hypothermic patient are practically unknown. When a blood sample is cooled anaerobically the PCO_2 decreases and the pH increases in a predictable manner, which has been formulated(2) and is applied by clinicians to correct the pH and PCO_2 values measured with electrodes maintained at 37°C. At the same time it has been shown(3) that **in vivo** changes in pH and PCO_2 in ectotherms are similar to **in vitro** changes which take place in an anaerobic sample of blood that is cooled. Evidence has been presented that the correct intracellular pH during hypothermia is the pH of electrochemical neutrality of water (where pH = pOH), which is 6.80 at 37°C, with body fluids maintained at 0.6-0.8 pH units to the alkaline side of this.

The buffering capacity of the extracellular fluid system involving the unique properties of the protein buffer -- **imidazole of histidine,** and the precise regulation of the bicarbonate buffer help to maintain acid-base balance with changing t° on both sides of the cell membrane.

In ectotherms as well as in homeotherms it is the hydroxyl-hydrogen ion concentration ratio (OH^-/H^+) that is defended in normal acid-base regulation, so that a constant protein net charge of the intracellular compartment is preserved. We decided to study the importance of maintaining euthermic ventilation in hypothermic patients.

Methods. Fifty four patients (33 male and 21 female) 41-85 years old (mean = 64) who underwent open heart surgery with hypothermia were studied. Blood gases were determined prebypass, during hypothermia and postbypass. Measurements (not corrected for t°) were done with the electrode maintained at 37° C. All data are expressed as the mean value and standard error of the mean.

Results. Initial slight hypocapnia with moderate reduction in HCO_3^- content was due to excessive ventilation at the beginning of surgery with a pH value of 7.42 ± 0.8. Normal pH values (7.45 ± 0.6) were obtained during cardiopulmonary bypass with hypothermia. During the rewarming process the pH values were 7.40 ± 0.5. Constant pH values measured at 37° C prove that constant OH^-/H^+ ratio was present at all t°-s. Prebypass $PaCO_2$ was 35.2 ± 8.7 mmHg which remained at a steady level of 36.0 ± 6.0 mmHg during the hypothermic bypass period and was equal to 35.0 ± 8.0 mmHg during the rewarming process. The prebypass value of HCO_3^- was 22.3 ± 4.2 meq/L which went up to a value of 24.4 ± 2.9 meq/L during the period of hypothermic bypass and returned to a value of 22.6 ± 2.3 meq/L for the rewarming period. A significant buffer concentration difference could not be found before, during or after cardiopulmonary bypass.

Discussion. If ventilation is kept constant the "internal milieu" of a patient will reveal pH and PCO_2 curves, where optimal conditions will be provided to preserve intracellular neutrality.(4) This requires that **no CO_2 be added** to the inhaled gas mixture during hypothermic cardiopulmonary bypass. The rate and volume of each respiration should approximate those of normal alert breathing, which should create a moderate relative hyperventilation as metabolic CO_2 production is suppressed by cold. If the measurements at 37°C are in the normal range (i.e. pH = 7.40 ± 0.04 and PCO_2 = 40 ± 4.0 mmHg), we are satisfied that the patient's acid-base status is acceptable, and any adjustments are based on "uncorrected" values irrespective of the patients' actual t°.

Observations of the behavior of human blood (outdoor exercise on a cold and windy day) could be made by comparing pH of blood from skin capillary 25°C, heart 37°C, and exercising muscle 41°C. Observed pH values of 7.60 in skin and 7.35 in muscle confirm that, in arterial blood the OH^-/H^+ ratio has been held constant within this t° range. It is important to note that human blood, even when core t° is normothermic, has a spectrum of pH values.(5) Literature data and our clinical findings suggest that one should try to maintain a constant CO_2 content of the blood, a normal Donnan ratio between plasma and cells, a tissue pH close to neutrality, and, last but not least, a constant net charge of the protein buffer, **imidazole of histidine.**

In practice it means that ventilation should be maintained at or near the euthermic setting as the body is cooled. To monitor and maintain adequate ventilation one need only withdraw a blood sample, rewarm it immediately and obtain a pH and PCO_2 reading with an electrode kept at 37°C. If a pH value is similar to the previous normothermic data e.g., 7.40 then the desired ventilation and PCO_2 are achieved to maintain a constant relative alkalinity. If such a patient's blood had been withdrawn at a core t° of 20°C and analyzed at that t°, the pH would have been 7.65 and the PCO_2 18 mmHg if the intracellular neutrality had been preserved. However, if that sample had been quickly rewarmed, anaerobically, and measured at 37°C, the pH would then read 7.40 and the PCO_2 40 mmHg.

References.

1. Nunn JF. Applied respiratory physiology, 2nd ed. London, Butterworths, 1977, p 347.
2. Severinghaus JW. Blood gas calculator. J Appl Physiol 1966; 21:1108-1116.
3. Howell BJ, Baumgardner FW, Bondi K, et al. Acid-base balance in cold blood vertebrates as a function of body temperature. Am J Physiol 1970; 218:600-606.
4. Rahn H, Reeves RB, Howell BJ. Hydrogen ion regulation, temperature, and evolution. Am Rev Respir Dis, 1975; 112:165-172.
5. Ream AK, Reitz BA, Silverberg G. Temperature correction of PCO_2 and pH in estimating acid-base status. Anesthesiology 1982;56:41-44.

TITLE: CAN RESPIRATORY ALKALOSIS DELAY VENTRICULAR FIBRILLATION DURING HYPOTHERMIC CARDIOPULMONARY BYPASS?

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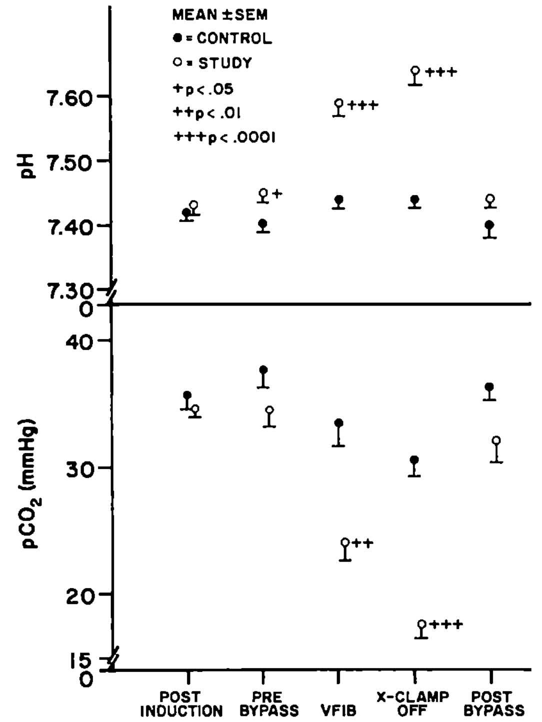
Introduction. Myocardial preservation, essential for cardiac surgery, could perhaps be improved by delaying the onset of ventricular fibrillation (VF) during cooling on cardiopulmonary bypass (CPB). This human study questions what effect respiratory alkalemia has on temperature level (T) and time at which VF occurs during hypothermic CPB.

Methods. After approval by Research Review Committee and informed consent, 16 adults (49-78 yrs) undergoing elective myocardial revascularization were randomly assigned to control (n=8) or study group. An arterial line and Swan-Ganz catheter were placed in each patient. Anesthetics consisted of fentanyl, oxygen, isoflurane, and pancuronium. pH uncorrected for T was kept at 7.4 pre and postbypass. At the outset of CPB both groups were actively cooled. The surgeons refrained from handling the heart until VF occurred. The control group was kept at pH 7.6 by reducing the pCO2 in the bypass circuit. During surgery, hemodynamics, T's (esophagus, blood, bladder), arterial blood gases, potassium, hemoglobin, glucose, albumin, free fatty acids, lactate, epinephrine, norepinephrine and insulin were measured. Statistical analysis was accomplished by the use of Student's T test and two-way analysis of variance.

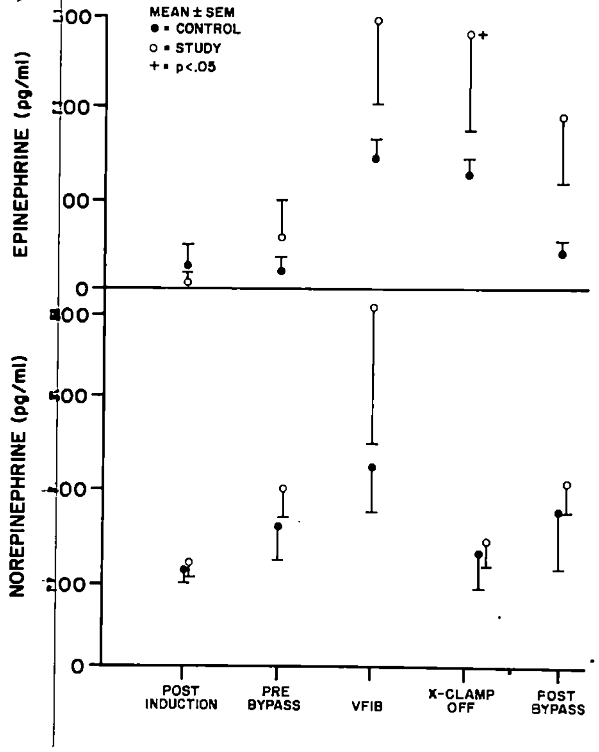


Results. Anesthetic and surgical outcome were satisfactory in both groups. Mean arterial, right atrial and pulmonary artery pressures, cardiac output and systemic vascular resistance were acceptable and similar in all patients. T's at the study points were not statistically different. Blood T in the control group at the time of VF was 23.5±0.9°C and in the study group 21.7±0.5°C. Time from onset of CPB to VF in the controls was 9.8±1.4 min compared to 11.4±1.3 min, not statistically significant. Comparing all study points, potassium, hemoglobin, glucose, albumin, free fatty acids and insulin were alike. During CPB the study group's lactate levels were higher ($p<0.05$). pH, pCO2, epinephrine and norepinephrine levels are as shown below.

Discussion. If alkalemia during CPB was of metabolic advantage then the heart should maintain a rhythm longer and achieve a lower T at VF. This was not the case. It is not possible from this study to say whether the rise in lactate is from inhibition of hepatic utilization or increased production by peripheral tissues. The reason for the elevation of epinephrine also is beyond the scope of this study. What can be concluded, however, is that in these humans, unlike animal studies, there was no metabolic advantage in maintaining alkalemia during hypothermic CPB (1).

References.

1. Becker H, Vinten-Johansen J, Buckberg GD et al.: Myocardial damage caused by keeping pH 7.40 during systemic deep hypothermia. J Thorac Cardiovas Surg 1981 82:810.



Title: **EFFECT OF NALBUPHINE IN CANINE HEMORRHAGIC SHOCK**

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Introduction. Endogenous opioid systems have been implicated in the deleterious effects of both endotoxic and hemorrhagic shock. Naloxone has been utilized to improve cardiovascular function in circulatory and septic shock with occasional improved survival. However, naloxone can block pain relief from endorphins and may override beneficial effects. An agonist-antagonist drug, nalbuphine, may be useful in preserving cardiovascular effects of naloxone, while at the same time maintaining analgesic effects of narcotics. We hypothesize that nalbuphine maintains the efficacy of hemodynamic preservation of narcotic antagonists in the presence of hypovolemic shock while ameliorating the cardiovascular depression associated with pure narcotics in the hypovolemic state.

Methods. Male mongrel dogs weighing 18-25 kg were anesthetized with 30 mg/kg pentobarbital, intubated and allowed to breathe spontaneously. Lead II EKG and heart rate were monitored continuously. Bilateral femoral incisions were made and a 7 French Swan-Ganz catheter was inserted into the pulmonary artery via the right femoral vein to measure pulmonary artery pressures (PAP) and pulmonary artery wedge pressure (PCW). Cardiac output (CO, L/min) was determined in duplicate by thermodilution. The right femoral artery was cannulated with a 5 Fr catheter and inserted into the aorta for determination of mean arterial pressure (MAP). A pigtail catheter was inserted into the left ventricle via the left femoral artery. The left ventricular pressure signal was differentially amplified to record rate of change of left ventricular pressure (dp/dt). Supplemental pentobarbital (1-2 mg/kg) was administered as needed. Core temperature was maintained at 37±1°C using heating lamps. Blood samples were obtained periodically for hematocrit, electrolyte and blood gas analysis. After a 30 minute baseline period, dogs were heparinized (5000 U, IV) and bled into a reservoir until a MAP of 40 mmHg was obtained. MAP was maintained at this level for an additional 60 minutes by infusing or removing further blood. At 60 minutes post hemorrhage, the reservoir was clamped, and the animal received either 0.9% NaCl or nalbuphine 1 mg/k, 10 mg/k, 50 mg/k as a slow IV bolus through a peripheral vein. Hemodynamic measurements were obtained at 5, 10, 15, and 30 minutes following drug infusion and every 30 minutes thereafter. All drugs were administered so that the animals received the same volume of diluent.

Results. No significant differences were noted in any hemodynamic measurements in control and treated animals prior to administration of nalbuphine. In addition, no statistically significant variation was noted until 30 min following drug infusion, when MAP and dp/dt were elevated above control. CO was also elevated, but was not significant (Table 1). A clear prolongation of acute survival time in animals treated with nalbuphine (10 mg/k and 50 mg/k) was observed (Table 2).

Discussion. Nalbuphine in doses of 10 mg/k and 50 mg/k prolonged acute survival in dogs subjected to hemorrhagic shock from 117±7 min to 158±35 min and 204±18 min respectively. Significant differences were noted for MAP and dp/dt 30 min following nalbuphine administration. CO approached, but did not reach, statistical significance at 0.05 level. There was no alteration in PCW, HR or TPR among or between treatment groups (data not shown).

The interaction of nalbuphine at several opiate receptors may partially explain its beneficial effects in shock. Nalbuphine analgesia appears to be subserved by partial agonism at the kappa receptor and also as a weak mu receptor antagonist. These weak antagonist properties may account for its ameliorative effects in shock, while preserving analgesia. Thus opiate agonist-antagonist analgesics with agonist properties may prove useful in the management of shock.

Table 1: Effects of Nalbuphine 30 min after infusion following 1 hr of hemorrhagic shock.

Treatment	CO	MAP	PCW	HR	dp/dt
Control	.67	25	1.25	169	.956
Nalbuphine					
1 mg/kg	.91	51*	2.00	158	1.935*
10 mg/kg	1.39	74*	0	189	1 667*
50 mg/kg	1.19	59*	3.25	163	2.502*

* = $p<0.05$, n = 4 following one way analysis of variance and multiple comparison procedures.

Table 2: Nalbuphine effect on survival time of animals subjected to hemorrhagic shock.

Treatment	Time of Death (min)
Control	117 ± 7
Nalbuphine	
1 mg/kg	111 ± 16
10 mg/kg	158 ± 35*
50 mg/kg	204 ± 18*

* = $p<0$ 05 ,n = 5 analyzed according to Table 1.

Title: ISOSORBIDE DINITRATE VS NITROGLYCERIN FOR THE CONTROL OF PERIOPERATIVE HYPERTENSION

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Introduction Perioperative hypertension is frequently encountered in patients undergoing coronary artery bypass surgery (CABG). Kaplan et al have demonstrated the efficacy of nitroglycerin (NTG) in the treatment of acute hypertension during CABG (1). More recently, intravenous isosorbide dinitrate (ISDN), a more stable nitrate preparation, has become available and has been used successfully in the postoperative management of cardiac surgical patients. The aim of this study was to compare the efficacy of ISDN and NTG for the treatment of perioperative hypertension in patients undergoing elective CABG. For this purpose, a large multi-center study was initiated.

Methods After institutional approval had been given at each of the three participating institutions, informed consent was obtained from 85 patients scheduled for elective CABG. The patients were randomly assigned to an ISDN or NTG group and the study was conducted in a double-blind manner. On the day of surgery, the patients were premedicated with morphine sulfate (0.15 mg/kg) and scopolamine (0.4 mg) IM. Ninety minutes later, under local anesthesia, a radial artery catheter, a thermodilution pulmonary artery catheter, and intravenous catheters were placed percutaneously. Control hemodynamic measurements were then made of heart rate (HR), systolic (SAP), diastolic (DAP), and mean (MAP) pressure, right atrial pressure (RAP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), thermodilution cardiac output (CO), arterial and mixed venous blood gases. General anesthesia was induced with fentanyl 75 ug/kg, and the patients were ventilated with 100% oxygen. Endotracheal intubation and muscle relaxation were facilitated by the use of pancuronium bromide (0.15 mg/kg). Based upon the control systolic blood pressure (SBP), an SBP "trigger" value was defined for each patient. An infusion of either ISDN or NTG was begun whenever SBP exceeded this trigger value. The infusion was started at 0.5-1.0 ug/kg/min and gradually increased to a maximum infusion rate of 10 ug/kg/min. A treatment success was defined as return of systolic blood pressure to control. A treatment failure was defined as continued elevation of blood pressure to a predetermined failure value. The study was conducted in three phases: before cardiopulmonary bypass (CPB), after CPB, and during the first 4 hours after admission to the ICU. All the results are expressed as mean±SD and the differences were tested for statistical significance by ANOVA.

Results 43 patients were randomized to the ISDN group and 42 to the NTG group. No significant intergroup differences in demographic variables were observed. A total of 245 events in which SBP exceeded the trigger value were observed. 60% of these events occurred before CPB, 13% after CPB, and 27% in the first 4 hours after admission to the ICU. Patients in the ISDN group had an average of 2.4 events per patient versus 3.8 events per patient in the NTG group. The SAP, DAP, and MAP were significantly lower after treatment with either drug (see table). NTG also produced a small but significant increase in HR and decrease in CO. The treatment was considered a failure in 39% of events treated with ISDN versus 17% of events in the NTG group.

Discussion In most studies, NTG has been found effective in controlling hypertension and beneficial because of its effects on intercoronary collateral blood flow in the presence of regional ischemia. Under the circumstances of this study, ISDN also lowered high systemic pressure, but to a lesser degree than NTG and in fewer hypertensive episodes. A possible benefit of ISDN was a lack of significant changes in heart rate and cardiac output. In conclusion, these results indicate that both ISDN and NTG can safely be used in the treatment of perioperative hypertension.

Reference
1. Kaplan JA, Dunbar RW, Jones EL: Nitroglycerin infusion during coronary artery surgery. Anesthesiology 45:14, 1976.

TABLE

	NTG		ISDN		
	Pre	Post	Pre	Post	
SAP (mmHg)	160±14	130±24@	155±17	138±19@	
MAP (mmHg)	106±14	88±15@	104±15	93±14@	
DAP (mmHg)	79±14	60±13@	79±13	72±12@	
PCWP (mmHg)	10±5	7±4@	12±5	9±4@	
C.O. (L/min)	5.1±1.6	4.8±1.5*	4.9±1.5	4.8±1.5	N.S.
HR (BPM)	76±29	79±17#	73±17	74±15	N.S.
SVR (dynes sec cm^{-5})	1709±657	1482±575@	1715±703	1594±523*	

* $p < 0.05$ # $p < 0.01$ @ $p < 0.001$

Title: LUNG PROTECTION IN CHILDREN DURING EXTRACORPOREAL SHOCK-WAVE LITHOTRIPSY

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Introduction. Extracorporeal shock-wave lithotripsy (ESWL) has become a mainstay in the treatment of urolithiasis in Europe and the United States. The application of shock-wave (SW) treatment in children with urinary calculi poses particular problems. Adjustment of water level and of the ESWL frame designed for adults are not problematic. The most serious difficulty is due to the proximity of the kidneys to the lungs in children. Though the renal and surrounding tissues are quite resistant to damage by repeated SW, the lung is easily damaged by directly applied SW and may be injured even by unfocused SW on the periphery. Recommendations for protection of lung tissue based on experiments in animals include the interpolation of 0.3 cm thick styrofoam sheet between the source of SW and the lung tissue.[1] On being asked to anesthetize children for ESWL, we developed a system of general anesthesia (GA) including a method for protection of the lungs based on available animal experimental data.

Method. Preoperative preparation included detailed discussion with the parent(s) concerning the expected risks, and informed consent in all cases. Oral diazepam premedication in most cases preceded induction of GA with intravenous fentanyl and thiopental, or nitrous oxide, oxygen and volatile agent by mask. All patients were intubated following muscle relaxant administration and ventilated with nitrous oxide and oxygen ± volatile agent. Inspired oxygen concentration (F_IO_2), oxygen saturation by pulse oximeter, expired partial pressure of carbon dioxide ($PECO_2$), nasopharyngeal temperature and automated arm blood pressure were monitored continuously and recorded. Shock-absorbing material consisting of styrofoam sheet greater than 1 cm thick was securely taped to the ESWL frame, providing both support and lung protection. In one case, a circular opening about 12 cm in diameter was made in the styrofoam sheet and an attempt was made to position this opening directly over the source of SW. Triggering of SW 20 milliseconds after the R wave of the ECG was utilized to limit the possibility of ventricular dysrhythmias seen in early studies in adults. Ventilation occurred only between episodes of SW application, in order to limit lung excursion into the field, and each series of shock-waves began only after the $PECO_2$ had again fallen below 30 mmHg.

Results. Of 801 patients given GA on 935 occasions, eight were children aged 13 or less, who had a total of ten ESWLs. The table shows the collected data for these patients. Induction to immersion times ranged from 5 to 9 minutes, except in the smallest child, where 36 minutes were needed for satisfactory anesthesia induction and positioning. The actual time taken for SW applications averaged 35.4 minutes (30.5 in adults). The lowest O_2 saturation was 94%; the highest F_IO_2 0.40. Temperature increased in all cases, an average of 0.3°C. All were extubated within 7 minutes of emersion from the ESWL tub. None had hemoptysis, chest pain, chest X-ray evidence nor any other clinical evidence of pulmonary contusion. In one 9-year-old, in whom styrofoam sheet with a circular opening was used, the stone failed to significantly fracture and a second ESWL was required. On the second occasion, lung protection was achieved by the use of a soft foam sheet with adhesive backing (Reston™, 3M) applied directly to the skin over the ipsilateral lung. No clinical signs of pulmonary damage were seen, and the stone was completely fragmented.

Discussion. Severe pulmonary damage in animals following a single shock-wave provides cause for great concern in children undergoing ESWL. Anecdotal accounts of pulmonary hematoma in a child during ESWL suggest that the risk may be substantial, and lung protection by shock-absorbent material a logical precaution in these children. We initially used a styrofoam sheet more than three times thicker than that which had given protection in animals. Later in the series, enthusiastic use of protective shielding apparently caused sufficient attenuation of the shock-wave to prevent adequate stone fragmentation. Following clinical tests in volunteers, a soft adhesive-backed foam applied directly to the patient gave adequate protection while allowing successful treatment. The use of an apneic technique during actual SW application, though not studied in detail, appears to be a logical precaution especially in smaller children. None of our patients had clinical evidence of pulmonary pathology following ESWL. Even a child as small as 10.5 kg was able to safely benefit from what is certainly a major improvement in the treatment of urolithiasis.

Age of Patient	Weight (Kgs.)	ASA Status	No. of Shock Waves
10	23.7	1	1500
9	31.8	1	900
13	75	2	1200
2	10.5	3	600
13	44	1	1600*
10	31.5	1	1000
11	40.8	2	1250
9	25.4	1	2000*

*Total for two procedures

Reference

1. C. Chaussy (Ed.), KARGER (Publ.): Extracorporeal Shock Wave Lithotripsy, 1982

Title: KETAMINE POTENTIATES PANCURONIUM-INDUCED NEUROMUSCULAR BLOCK

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Introduction. Conflicting results have been reported on whether ketamine would potentiate the neuromuscular effect of pancuronium (1-2). Recently in a series of studies we found that ketamine enhances the neuromuscular block induced by d-tubocurarine, vecuronium and atracurium. Hence, the present study was undertaken to reevaluate the interaction on neuromuscular transmission between ketamine and pancuronium.

Method. The study was approved by the Institutional Review Board. Twelve adult monkeys (Macaca Cyclopis Swinhoe) weighing 5 to 8 kg were anesthetized with methohexital 10-15 mg/kg I.M. Two I.V. lines were inserted, one into each limb. Dextrose 5% in water was infused at 5 ml/kg/hr. Anesthesia was maintained with halothane 0.5% in oxygen and the trachea was intubated without use of muscle relaxant. The end-tidal CO_2 and halothane concentration were monitored and recorded with a Datex Normocap CO_2 monitor and a Datex anesthetic gas monitor. Ventilation was controlled with a mechanical ventilator to keep end-tidal PCO_2 at 30-40 mmHg. Esophageal temperature was maintained at 35-37°C. An arterial catheter was placed in the anterior tibial artery for recording blood pressure and for blood gas determinations. Arterial blood pH was controlled at 7.30-7.40. The ulnar nerve in the left wrist was stimulated at 0.3 Hz with Grass S-44 nerve stimulator using stimuli of 0.1 msec duration, at twice maximal voltage. Force of left thumb adduction was transduced by a Grass FT-03 force transducer. ECG, arterial pressure and thumb twitch were recorded simultaneously on a 4-channel polygraph recorder. After a stable anesthetic plane was established, ketamine was given at hourly intervals at a progressively increasing dose of 2, 5, 10, and 20 mg/kg intravenously to 5 monkeys of the control group. In 7 monkeys of the study group, 50% twitch depression was maintained by continuous intravenous infusion of pancuronium first. Then the same 4 doses of ketamine (2, 5, 10, and 20 mg/kg I.V.) was added sequentially, allowing full twitch recovery from effect of ketamine between doses. Ketamine and pancuronium were given through separate I.V. lines.

Results. Intravenous ketamine alone at all 4 doses showed no effect on the thumb twitch. When 50% twitch depression was first established and maintained by continuous I.V. infusion of pancuronium (0.03 ± 0.01 mcg/kg/min.), the addition of ketamine at 5, 10, and 20 mg/kg produced a significant ($p < 0.05$) further depression of the twitch in a dose-dependent manner (Fig. 1). The maximal twitch depression occurred within 20-30 minutes after ketamine administration.

Discussion. Our study demonstrates that in monkeys under basal halothane anesthesia the addition of ketamine in dose of 2 mg/kg I.V. had no effect on the neuromuscular block established by pancuronium. This finding is in agreement with that reported by Johnston, et al, who utilized a similar dose in humans. However, at higher doses of 5-20 mg/kg I.V. ketamine significantly potentiates the pancuronium-induced neuromuscular block. Such potentiating effect of ketamine has been attributed to decreased sensitivity of the motor end-plate by Cronnolly, who demonstrated in frog sartorius muscles that ketamine reduced miniature end-plate potential amplitude and decreased the end-plate sensitivity to iontophoretically applied acetylcholine (3). We concluded that pancuronium-induced neuromuscular block in anesthetized monkeys is potentiated by I.V. administration of ketamine in a dose-dependent manner. The clinical implication of such synergistic effect must be borne in mind when the two drugs are used concomitantly.

References.

1. Amaki Y, Nagashima H, et al: Ketamine interaction with neuromuscular blocking agents. Anesth Analg 57:238-241, 1978.
2. Johnston RR, Miller RD, Way WL: The interaction of ketamine with d-tubocurarine, pancuronium and succinylcholine in man. Anesth Analg 53:496-501, 1974.
3. Cronnolly R: Interaction of ketamine HCl with neuromuscular agents. Fed Proc 31:535, 1972.

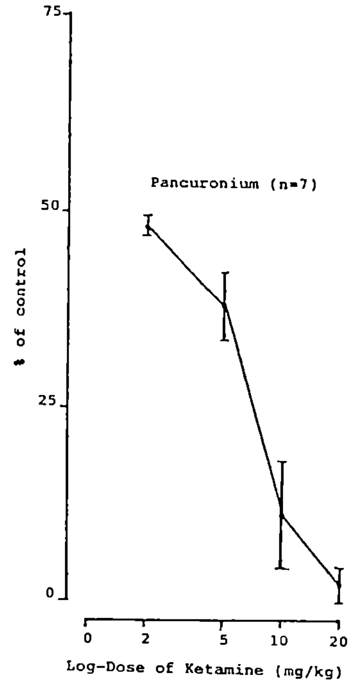

Fig. 1 The acute effect of I.V. ketamine administration on the pre-existing 50% twitch depression of the thumb adduction produced by infusion of pancuronium (vertical bars indicate stand deviations).

Title: EFFECTS OF NITROUS OXIDE DURING VENTRICULAR AND CORONARY AIR EMBOLISM IN SWINE

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Introduction: Coronary air embolism (CAE) is a major complication of heart surgery. Air can enter the coronary circulation during aortotomies for proximal coronary revascularization, valve replacements and during aortic cannulation for bypass. Once CAE has occurred, the severity of sequalae depends on the amount of air in the coronary system. N_2O has been shown to cause global as well as regional myocardial dysfunction in both humans and lab animals with lesions that limit coronary blood flow.(1,2) This study was performed to examine the cardiac effects of ventricular and CAE in the presence and absence of N_2O. We also tested the hypothesis that discontinuing N_2O after CAE occurs would improve cardiac performance and lessen the insult otherwise seen.

Methods: Overnight fasted (23 ± 7 kg) Hampton-Landrace swine were anesthetized with ketamine (25 mg/kg) and ventilated with 100% O_2. One group of pigs (N=7) were ventilated with air/O_2 (FIO_2=.33) for 15 minutes and then baseline values of blood gases, cardiac output, LV dp/dt, BP, HR, LVEDP as well as epicardial ECG were obtained. The inspired gas was changed to 100% O_2 and the same values recorded 1, 2, 3, 5, 10, and 20 minutes later. The inspired gas was then changed to air/O_2 (FIO_2=0.33) for 15 minutes, repeat measurements made, then a left ventricular air embolism (VAE) was administered at 0.01 cc/kg/min for 3 minutes (or less if CO reached 0; electromagnetic aortic flow probe), while the inspired gas was simultaneously changed to 100% O_2. The above data was then collected 1, 2, 3, 5, 10, and 20 minutes later. Another group of pigs (N=7) were ventilated with N_2O/O_2:(2/1) following the same protocol, substituting N_2O for air.

In the second phase of study, pigs (N=4) received CAE by injecting 0.01 cc/kg directly into the LAD coronary artery just distal to the first diagonal branch. The pigs were ventilated with an FIO_2=0.33 for 15 minutes and then had CAE administered while the inspired gas was changed to 100% O_2. Measurements of epicardial ECG's, proximal LAD blood flow (electromagnetic) aortic blood flow, LVdp/dt, LVEDP, BP, HR and blood gases were made pre CAE and 1, 2, 5, 10, and 20 minutes post CAE. One half of these pigs received N_2O/O_2 during the 15 minute period pre CAE, the other half received air/O_2. Data for blood gases and emboli volumes were analyzed using paired and unpaired t tests. Physiologic data was analyzed using ANOVA with repeated measures in 2 variables.

Results: Prior to VAE, the N_2 and N_2O groups did not differ in weight, MAP, PA, LVEDP, CO, dP/dt or blood gas analysis. After VAE all cardiovascular parameters were depressed with a gradual return toward baseline in surviving animals in both groups. The volume of air infused was similar between the groups. Four of the seven animals in the N_2O group and none of the seven in the air group died in ventricular fibrillation within 15 minutes following air emboli (p=.035). One animal in the air group expired at 19 minutes following VAE. Physiologic variables between the 3 animals that survived VAE in the N_2O group and the 6 in the air group were not significantly different over time. CAE resulted in immediate abolition of coronary blood flow in the presence of air as well as N_2O. In the air ventilated animals, recovery toward pre-CAE control values occurred over 15 minutes. In the N_2O group both animals died in ventricular fibrillation with 5 minutes following CAE. The length of LAD segment containing gas and the area of ischemic myocardium was abserved to be far greater in the N_2O than in the air group following CAE.

Discussion: The cardiovascular insult from ventricular as well as coronary air embolism is enhanced in the presence of N_2O. The cardiovascular insult after CAE appears to be due to decreased coronary blood flow, which is worsened in the presence of N_2O. This is probably due to expansion of the air embolus, an easily visualized phenomena. Our data reconfirm that there is no significant effect of N_2O on nonischemic myocardia. Our data also suggests that N_2O should not be used whenever there is possibility of ventricular or coronary air entrapment, since even after discontinuing N_2O at the time of air embolization neither the cardiovascular insult nor the mortality were lessened.

Table 1: Ventricular Air Embolism

Min p VAE	0	1	2	3	5	10	20
N_2	1530	870	915	1000	960	970	1415
DP/DT	±810	±580	±615	±600	±560	±475	±725
N_2O	1190	410	830	700	560	850	1470
	±650	±320	±1270	±725	±480	±465	±680
N_2	2.0	.8	.6	.6	.7	.6	1.1
CO	±.2	±.4	±.3	±.4	±.3	±.4	±.4
N_2O	1.2	.1	.3	.4	.3	.3	.5
	±.6	±.1	±.3	±.4	±.5	±.5	±.8
N_2	8.2	9.6	9.3	9.6	11.8	10.4	8.7
LVEDP	±5.7	±4.7	±4.3	±3.7	±5.9	±5.1	±6.5
N_2O	6.8	12.9	13.8	12.0	9.4	10.6	10.0
	±2.8	±3.0	±4.7	±4.5	±5.1	±5.9	±10.0

Values are means ± SD

Table 2: Coronary Air Embolism

Min p CAE	Pig #		0	1	2	5	10	20
N_2	1		2.5	.8	.8	.8	1.5	2.5
	2	CO	2.5	2.2	2.3	2.3	2.5	2.5
N_2O	1		2.6	1.7	1.5	---	---	---
	2		1.7	1.4	---	---	---	---
N_2	1		3600	3350	3300	3400	3500	3700
	2	dP/dt	2000	1200	1250	1250	1750	1750
N_2O	1		3600	2100	3000	----	----	----
	2		4400	3500	----	----	----	----
N_2	1		43	16	21	40	48	45
	2	CBF	22	0	2.5	5	22	45
N_2O	1		24	8	7	--	--	--
	2		20	0	--	--	--	--

References:

1. Philbin DM, Foex P, et. al: Postsystolic shortening of canine left ventricle supplied by stenotic coronary artery when N_2O is added in the presence of narcotics. Anesthesiology 1985;62:166-74.

2. Balasaraswathi K, Kuman P, et. al: LVEDP as an index for N_2O during coronary artery surgery. Anesthesiology 1981;55:708-9.

Title: DOES EUVOLEMIC CRYSTALLOID REPLACEMENT OF BLOOD LOSS PRODUCE HYPOCOAGULABILITY?

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Introduction: The thromboelastograph (TEG) has been shown to be of clinical utility in the evaluation of the whole blood hemostatic process in the operating room.(1) TEG is routinely used during hepatic transplantation procedures(2) and at our institution has been used with success to predict non-surgical post-operative bleeding in cardiac surgical patients. The TEG monitors coagulation from the formation of the first fibrin strands through fibrin cross-linking and clot retraction to eventual clot lysis. Measurement of coagulation factor function, platelet abnormalities and clot integrity can be determined from this single test. The purpose of this study was to examine the effects of moderate blood loss and crystalloid replacement on TEG parameters (R, K, MA, AD).

Methods: After approval by the institutional Human Investigations Committee 68 adult subjects undergoing major orthopedic, abdominal, cranial, thoracic and gynecological procedures were entered into the study. All patients were treated with standard anesthetic and surgical techniques. All patients received general anesthesia with isoflurane or halothane in O_2/N_2O (1:1). Intravenous agents used included etomidate, thiopental and fentanyl. None of the patients had any preoperative alterations in coagulation either clinically or by measurement of PT, PTT, fibrinogen, and platelet counts. No patients were receiving anti-coagulant or anti-platelet medications.

Blood samples for TEG analysis were obtained 5 minutes before and after induction of anesthesia, when EBL=0.05 EBV, 0.10 EBV, 0.15 EBV, at end of surgery and 2 hours postoperatively. The total volume of crystalloid and blood administered at this time were noted. Measurements of TEG parameters R, K, AD and MA were performed on all samples (Biclot Elvi 816). Patients receiving blood (N=27) had TEG measurements made before and after transfusion. TEG parameters were considered jointly dependent and analyzed using Hotelling's T's. Repeated measures data was analyzed using MANOVA. Statistical significance was accepted with $p < 0.001$.

Results: This study demonstrates a tendency towards hypocoagulability after induction of anesthesia, as evidenced by prolongation of R. Moderate blood loss (0.05 EBV, 0.10 EBV) was accompanied by hypercoagulable TEG parameters compared to postanesthesia controls (decreased R and K, increased AD and MA). An additional increase in coagulability was seen in patients experiencing 0.15 EBV loss. TEG parameters (R, K, AD, MA) all returned to preanesthesia/surgery levels by the end of operation and remained so 2 hours postoperatively.

Accounting for NPO fluid deficits, the data indicate that crystalloid replacement allowed for euvolemic blood loss in both groups.

TEG Parameters vs. Blood Loss

		R	K	AD	MA	Fluid Replace/EBVL
Preanesthesia		20±2	11±1	44±2	55±2	
Postanesthesia		31±4	13±2	40±3	52±3	
5%	A	23±1	10±0.5	46±1	55±1	
	B	23±2	10±1	48±2	55±2	
	C	26±4	9±2	47±7	55±5	.66
10%	B	23±4	10±1	48±2	57±2	
	C	28±5	11±2	42±7	54±4	.69
15%	C	20±4	10±1	45±5	54±4	.81
End of Care		21±1	9±1	49±2	51±2	
2 hr postop		20±1	11±1	48±2	49±3	

Total EBVL 0.05=GRP A (N=68) 0.10=GRP B(N=15)
0.15=GRP C (N=5)
Values are means ± SEM

Discussion: The TEG parameter R measures the times it takes for fibrin strands to form; K and AD reflect the speed at which fibrin strands cross-link until a consolidated clot is formed. The strength of the consolidated clot is reflected by the MA value, which depends on platelets and fibrinogen. A hypercoagulable state would be reflected by a decrease in the R and K values with an increase in the AD and MA values, as reflected in our results.

Hemodilution and loss of coagulation factors and platelets during blood loss replaced with crystalloid might suggest that a hypocoagulable state might result. However, it is likely that surgical stress, tissue trauma and elevations in serum catecholamines offset this and result in accelerated coagulability,(3) despite the effects of general anesthesia. In conclusion, moderate euvolemic blood loss without blood or blood product replacement during general anesthesia has been demonstrated to result in intraoperative hypercoagulability with a postoperative return toward the preoperative coagulation state. Based on these results, there appears to be no justification for factor or platelet administration during euvolemic crystalloid replacement of moderate blood loss.

References:

1. Howland WS, Schweitzer O, Gould P: A comparison of intraoperative measurement of coagulation. Anes Analg 1974;53(3):657-663.
2. Kang YG, Martin DJ, et al: Intraoperative changes in blood coagulation and thromboelastographic monitoring in liver transplantation. Anes Analg 1985;64:888-986.
3. Sokolov EJ, et. al: The effects of stress on intravascular coagulation in patients with angiographic evidence of coronary disease: Kardiologia 1985;25(2):34-38.

Title: **PROLONGED ANESTHESIA WITH NITROUS OXIDE: IS IT HAZARDOUS?**

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Introduction. The traditional image of N_2O as a benign anesthetic has been tarnished in recent years by the documentation of several deleterious effects, including a decreased ventilatory response to hypoxia, atelectasis, fetal hypoxia, increased sympathetic activity, expansion of gas-containing spaces, nausea, and an inhibition of methionine synthetase with the potential for leukopenia and teratogenicity.[1] While these effects have been documented, usually during conditions of chronic exposure to the gas, their impact on the outcome of patients having routine surgical anesthesia remains undocumented. If indeed, N_2O is hazardous, we hypothesized that clinical evidence of adverse effects would be most obvious in patients undergoing prolonged anesthesia. Consequently, we retrospectively examined numerous variables of patients exposed to prolonged general anesthesia, with and without N_2O, to determine whether or not there was a difference in the intraoperative or postoperative course.

Methods. After approval by the Human Subjects Review Committee, 84 patients who underwent anesthesia for longer than 10 hours were identified using the department's computerized anesthesia database.[2] Excluded from consideration were (a) patients anesthetized for labor and delivery, thoracic or abdominal surgery, (b) patients who expired within 3 weeks of the anesthetic, and (c) those cases where the inhaled agent was changed during the anesthetic. Records were reviewed for preoperative, intraoperative, and postoperative variables, including temperature, blood pressure, heart rate, blood cell counts, liver function tests, blood loss, fluid therapy, urine output, and renal function tests. In addition, we noted complications including wound infection, pneumonia, pressure injuries, the need for postoperative ventilation, and prolonged hospitalization. To minimize the possible influence of the type of surgery, we limited our analysis to patients undergoing craniotomy with a total blood loss of less than 1000 ml. Of 30 patients having prolonged anesthesia and meeting the above criteria, 22 received N_2O and 8 did not.

Results. Although patients in the two groups did not differ significantly in terms of the length of anesthesia, age, operative procedure or blood loss, there were some differences noted between the two groups. The maximum temperatures during the 10-11th and 12-13th postoperative days were significantly higher (by approximately 1 degree) in the patients who did not receive N_2O. Similarly, these patients also had a significantly higher white blood cell count on post-op day 12 than did patients who received N_2O (mean of 15800 vs. 8600). Patients who received N_2O had a lower hematocrit on post-op day 2 (30.5% vs. 35.3%). However, patients receiving N_2O did not show evidence of increased sympathetic activity, morbidity from expansion of gas-containing spaces, or leukopenia. There were no differences between the two groups in terms of the number of wound infections, pressure injuries, pulmonary complications, days of postoperative mechanical ventilation, or length of hospitalization. There were insufficient data to permit statistical comparison of liver function tests between groups.

TABLE 1 (Mean ± SD)

	N_2O N = 22	NON-N_2O N = 8
ANESTHESIA TIME (MIN)	709 (±84)	765 (±137)
AGE (YEARS)	35.3(±14.9)	40.7(±18.5)
BLOOD LOSS (ML)	425 (±248)	328 (±248)
DISCHARGE DAY POST-OP	20.1(±19.1)	38.7(±47.2)
VENTILATED POST-OP	2/22	3/8
WOUND INFECTION	2/22	0/8
PRESSURE INJURY	2/22	2/8
PULMONARY INFECTION	3/22	3/8

Discussion. The potential for N_2O toxicity is clear. If N_2O is inhaled continuously for several days it can cause a fatal leukopenia. Chronic abuse of N_2O is associated with neurologic dysfunction, and daily inhalation of trace concentrations has been suggested as a cause for spontaneous abortion among O.R. personnel.

Despite these potential problems, we were unable to identify any untoward effects of N_2O when it was used to provide anesthesia for a group of patients undergoing operative procedures lasting longer than 10 hours. If toxicity from N_2O was to be a problem during routine clinical anesthesia, we would have expected evidence of same when patients are anesthetized for many hours. However, when patients who received N_2O were compared to a control group, we did not see evidence that N_2O was associated with hypertension, tachycardia, leukopenia, infection, neurologic dysfunction, laboratory evidence of organ toxicity, or prolonged hospitalization.

We conclude that a fear of toxicity from N_2O should not deter the anesthesiologist from using the drug during routine clinical anesthesia.

References.

1. Eger EI, NITROUS OXIDE/N_2O. Elsevier Science Publ Co, New York, 1985
2. Bashein G, Barna CR: Anesth Analg 64:425-431, 1985

Title: EFFECTS OF HIGH DOSE FENTANYL ANESTHESIA ON POSTERIOR TIBIAL NERVE SOMATOSENSORY EVOKED POTENTIALS

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Introduction. Posterior tibial nerve somatosensory evoked potentials(PTN-SSEP) are used to monitor spinal cord function during operations in which there is a risk of postoperative paraplegia. Balanced anesthesia using moderate doses of fentanyl, muscle relaxant and nitrous oxide is the technique of choice for PTN-SSEP monitoring. With this technique latencies are prolonged, while amplitudes are affected unpredictably (1). Resection of thoracic aortic aneurysms and correction of coarctation of the aorta are operations in which PTN-SSEP monitoring could be useful. High dose fentanyl anesthesia is an accepted technique for these procedures. We studied the induction effects of high dose fentanyl on PTN-SSEP and evaluated post-induction stability of latencies and amplitudes.

Methods. Ten patients, aged 23-70 years scheduled for elective non-coronary cardiac surgery gave informed consent to participate in the institutionally approved study protocol. None had evidence of neurologic or endocrine disease. Premedication was with lorazepam 4-5 mg orally and nicomorphine 0.15 mg/kg i.m. 1 hr before surgery. Anesthesia was induced with fentanyl 75 ug/kg. Pancuronium 0.1 mg/kg was given for muscle relaxation. After intubation of the trachea the lungs were ventilated with oxygen-air (FiO_2=0.5). Nasopharyngeal temperature, end-tidal CO_2, arterial and central venous pressures were continuously monitored. $PaCO_2$ was kept between 35-40 mm Hg. Prior to skin incision a second dose of fentanyl 25 ug/kg was given.

Recording technique. Cortical PTN-SSEP were recorded continuously using a Nicolet Pathfinder II. Posterior tibial nerves were stimulated bilaterally with constant current square wave pulses of 200 usec duration at a frequency of 3.1/sec. The stimulus intensity was 1 mA above the motor treshold; it was not changed after induction. Subdermal needle electrodes (impedance 6 Kohm) were inserted at Cz' referred to Fz for cortical recordings. Raw signals were filtered between 5 and 250 Hz. Analysis time was 160 msec. 512 sweeps were averaged. The following averages were analysed: immediately before and 5 min after induction, before and 5 min after the second dose of fentanyl, prior to cardiopulmonary bypass (CPB), and at the end of surgery. All data are expressed as mean ± SD. Statistical analysis was with one way ANOVA for correlated data. Differences between means were compared using a Tukey test.

Results. The induction dose of fentanyl increased cortical latencies of P1 (1.4±0.9msec), N1 (2.0±2.0msec), P2 (2.1±2.9msec) and N2 (10.6±4.5msec), although the increase in P2-latency was not statistically significant. The bolus dose of fentanyl (31±4 min after induction) caused no further increase of latencies. At the start of CPB (79±6 min after induction) P1, N1 and P2 latencies were not significantly different from the postinduction values, but N2 latency had increased further. All latencies were increased at the end of surgery. P1-N1 amplitude was unaffected by the induction dose, but N1-P2 amplitude was reduced by 50%. There was a gradual decrease in P1-N1 amplitude during the procedure, while N1-P2 amplitude remained at the post-induction value. The bolus dose of fentanyl did not change amplitudes.

Table: Latencies and amplitudes of PTN-SSEP before and during high dose fentanyl anesthesia (mean ± SD)

		LATENCY (msec)				AMPL. (uV)		TEMP.
		P1	N1	P2	N2	P1–N1	N1–P2	°C
before induction		42.7 ±5.32	49.1 ±5.90	63.7 ±5.82	86.4 ±8.14	2.20 ±1.57	3.84 ±2.03	–
after induction	a	44.2* ±5.61	51.1* ±6.94	65.5 ±7.73	97.0** ±6.70	2.22 ±1.99	1.83** ±0.88	36.3 ±0.42
before bolus	b	44.3 ±5.74	51.0 ±6.38	64.5 ±5.75	98.0 ±8.67	1.56 ±1.15	1.99 ±0.98	36.3 ±0.43
after bolus	b	44.9 ±6.01	51.5 ±6.56	66.5 ±6.42	99.9 ±7.93	1.36 ±0.97	1.71 ±0.80	36.2 ±0.48
before CPB	b	45.0 ±6.00	51.9 ±6.52	67.5 ±6.36	104.8** ±6.10	1.25* ±0.89	2.03 ±0.87	35.7* ±0.55
end of surgery	b	46.3** ±7.13	54.0** ±7.80	69.7** ±7.40	103.4** ±9.27	1.03** ±0.72	1.75 ±0.91	35.5** ±0.78

a = compared with pre-induction values * = $p < 0.05$
b = with values after induction ** = $p < 0.01$

Discussion. Induction with high doses of fentanyl causes relatively small increases in PTN-SSEP latency, while N1-P2 amplitude decreases. Despite the much higher doses of fentanyl used in this study the latency changes are less than reported with the thiopental/low dose fentanyl/ nitrous oxide technique. Pathak et al (1) reported an N1-latency increase of 4.4 ± 2.5 msec 30 min after induction compared to the 2.0 ± 2.0 msec found in this study. Furthermore, the subsequent bolus dose of fentanyl 25 ug/kg did not cause significant changes in either latency or amplitude. The latency increases before CPB and at the end of surgery can be explained partly by the gradual fall in temperature (2).
We conclude that high dose fentanyl with oxygen/ air is an excellent anesthetic technique when intraoperative PTN-SSEP monitoring is indicated.

References.

1. Pathak KS, Brown RH, Cascorbi HF, Nash CH. Effects of fentanyl and morphine on intraoperative somatosensory cortical-evoked potentials. Anesth Analg 1984; 63:833-7.
2. Rheineck Leyssius AT, Kalkman CJ and Bovill JG. Influence of moderate hypothermia on posterior tibial nerve somatosensory evoked potentials. Anesth Analg 1986; 65:475-80.

Title: **A COMPARATIVE EVALUATION OF PROPOFOL FOR THE INDUCTION AND MAINTENANCE OF GENERAL ANESTHESIA**

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Introduction: Propofol is a proven potent, safe anesthesia induction drug which has a rapid redistribution time (t½α 2.5 mins), rapid clearance, and an uniquely ultra-short β elimination (55 mins). The use of propofol by infusion appears to be appropriate for maintenance of anesthesia as well.

Methods: After IRB approval, three groups of ASA status I-III in- and outpatients undergoing elective gynecological surgery participated in an open, comparative, randomized study. There were no statistical differences between groups for age, sex, weight, BSA or ASA status. Surgical procedures included: 17 laparoscopies, 10 minilaparotomies for tubal ligation, 5 hysterectomies, and 14 other gynecological procedures. All patients were premedicated with meperidine, 1 mg/kg, and given curare, 3 mg/kg, 3-5 minutes prior to induction. They also all inhaled nitrous oxide 60% in oxygen. In group P patients, anesthesia was induced with propofol, 2 mg/kg followed by a continous exponential infusion based on the pharmacokinetic redistribution and elimination of the drug. When needed, the rate of infusion was modified to maintain adequate clinical anesthesia and to control hemodynamic parameters within 30% of baseline measurements. The average rate was 0.1-0.2 mg/kg/min. In group M patients, anesthesia was induced with methohexital, 1.5 mg/kg followed by an infusion of 0.1-0.3 mg/kg/min. In group TI patients, anesthesia was induced with thiopental, 4 mg/kg followed by isoflurane for maintenance (1.0-1.5%). Intubation was achieved with succinylcholine, 1.5 mg/kg, and muscle relaxation was maintained with pancuronium, 1-2 mg. In each group the appropriate induction agent was administered intravenously over 20-30 seconds, followed by the maintenance drug within 3 minutes. End-tidal CO_2 was maintained between 35-42 mmHg. Plasma levels of propofol were measured at 0, 2, 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180 and 240 minutes after anesthesia induction.

Results: Induction time (loss of eyelid reflex and cessation of response to command), duration of anesthesia, and recovery times are provided in Table 1. Groups P and TI patients showed similar hemodynamic responses to induction and maintenance of anesthesia. Blood pressure and heart rate decreased 15-20% from baseline for approximately 15 minutes after induction and subsequently fluctuated within 15-20% of baseline values. Blood pressure and heart rate were significantly higher in group M patients than in groups P and TI, ranging 20-30% during surgery above baseline values. The methohexital group demonstrated relatively unstable hemodynamics, delayed awakening, and postoperative respiratory depression. Two cases required prolonged postoperative mechanical ventilation. Also, 5 out of 14 patients had hiccups. The plasma levels of propofol at 2 minutes reflected the distribution of the bolus dose. Plasma levels of propofol during the infusion period were stable and confirmed the computer predicted stable levels; recovery phase (Stages III and V) revealed an exponential decline after discontinuation of infusion (Table 2). All patients were awake at 1 μg/ml plasma level and oriented at 0.6 μg/ml of propofol. Patients who received propofol had a tendency to wake up and respond quicker than patients who were maintained with isoflurane, but the difference did not reach statistical significance. Trieger test scores indicated faster recovery of coordination in group P patients compared to groups M and TI patients (Table 3).

Discussion: Propofol provides induction and maintenance of anesthesia with similar efficacy and safety compared to thiopental followed by isoflurane. The programmed infusion, which was based on a previously determined pharmacokinetic profile, proved to be an accurate guide for achieving stable blood levels, providing satisfactory clinical anesthesia and rapid recovery. In conclusion, we have demonstrated that intravenous infusion of propofol provides equal or better anesthesia than thiopental combined with isoflurane. Propofol infusion can rapidly achieve a steady blood concentration of the drug, adequate anesthesia and assure early recovery following discontinuation of the drug infusion. It seems that propofol infusion can provide optimal maintenance of anesthesia for both outpatients and inpatients.

Table 1.
Induction, Duration and Recovery Times
(Mean ± SD)

	Stage I	Stage II	Stage III	Stage IV	Stage V
P	43±12 (30-78)	80±47 (20-182)	5±3$^+$ (1-13)	6±4$^+$ (2-17)	18±10$^+$ (3-37)
M	35±13 (17-56)	36±15 (5-66)	21±21 (2-77)	22±22 (2-77)	34±22 (4-77)
TI	34±9 (18-52)	51±42 (13-178)	10±5* (3-21)	9±4$^+$ (3-20)	18±8$^+$ (5-35)

Stage I, induction time in seconds; Stage II, duration of anesthesia in minutes; Stage III, awakening, open eyes; Stage IV, response to verbal command; Stage V, orientation to place and date. P = propofol; M = methohexital; TI = thiopental/isoflurane. Range is presented in parentheses.
*$p < 0.01$, $^+p < 0.001$

Table 2.
Plasma Levels of Propofol in 7 Patients
(μg/ml) (Mean ± SD)

Stage I induction	Stage II maintenance	Stage III open eyes	Stage V orientation
3.1±1.1 (1.6-4.5)	2.3± (1.9-2.7)	1.0±0.2 (0.75-1.3)	0.6±0.2 (0.2-0.9)

(See table 1 for explanation of stages. Range is presented in parentheses.)

Table 3. Trieger Test Scores

	P	M	TI
Evaluation % completed at 60 minutes	78	78	88
Impairment time + accuracy ratio to baseline	0.71	0.16	0.5

P = propofol, M = methohexital, TI = thiopental/isoflurane

Title: DISTRIBUTION OF ^{3}H MORPHINE FOLLOWING LUMBAR SUBARACHNOID ADMINISTRATION IN RABBITS

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Introduction. Despite its popularity, the use of intrathecal(IT) morphine(M)(1) still poses questions such as how does it spread in the subarachnoid space (SAS), and what are the mechanisms for the long duration of action. This report concerns the investigation of the distribution of ^{3}H morphine (^{3}HM) following lumbar subarachnoid (LSAS) injection.

Method. Under N$_2$O + O$_2$ + Halothane endotracheal anesthesia, the cistern magna (CM) and LSAS of 3-4 kg New Zealand Albino rabbits were cannulated for sampling of cerebral spinal fluid (CSF) and administration of ^{3}HM respectively. One week after surgery, animals demonstrating intact neurological functions were divided into two groups. ^{3}HM was injected without anesthesia or other medications. Group 1 (n=5) received 200 ul of 0.26 mM (40 mg) M and 125 pM of ^{3}HM through an implanted PE 10 catheter in the LSAS. CSF (0.1 ml) was withdrawn from CM at 0, 5, 15, 30 minutes and 1, 2, 4, 12, 24 hours. Arterial blood was sampled at similar time intervals. Group 2 (n=11) was injected with 100 ug of M and 200 pM of ^{3}HM and blood and CSF were sampled as in group one; however, they were sacrificed under anesthesia at 2 hours (n=3), 4 hours (n=3), 6 hours (n=3) and 12 hours (n=2). The CNS was removed intact and 2 mm slices of spinal cord (SC) were removed at each 1 cm interval. These, and slices from various brain areas, were solubilized and counted with a liquid scintillation counter.

Results. The levels of ^{3}HM in the SC were highest at the lumbar injection site followed by a sharp decline over a distance of 4-5 cm and then a gradual decrease both cephalad and caudad.(Fig.1) Total recovery of radioactivity (RA) in the SC ranged: $\bar{X}\pm$SE 45% ± 5.57 for 2 hours, 12.8% ± 3.76 for 4 hours, 3.7% ± 1.13 for 6 hours and 2.45% for 12 hours. A significant amount of ^{3}HM was also detected in the spinal roots (SR) near the injection site. The bulk of the RA injected was recovered in the urine, and increased with time from a low of 30% of the injected ^{3}HM after 2 hours to a high of 75% after 12 hours. In group one and two no significant levels of RA were found in either blood or CSF samples. RA was not detected in the brain stem, cerebellum, caudate and frontal cortex slices.

Discussion. Our findings of the longevity of ^{3}HM in the SC and SR are consistent with its long duration of action. The ^{3}HM transferred from SAS to the blood might be diluted to levels beyond the sensitivity of our counting method. Renal concentration made it possible to measure ^{3}HM levels in the urine.

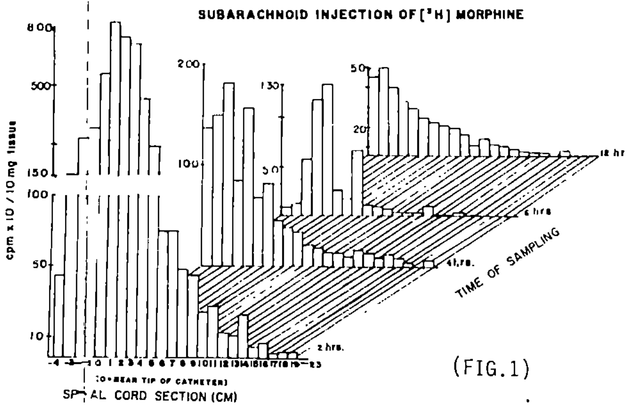
Using ^{14}C morphine autoradiography, Gustafsson et al (2) reported an increase in bladder size over time but did not describe levels of RA in the urine. Similiarly, levels of RA in the urine were not presented in other papers on ITM reviewed.(1,2,3,4,5,6)

Our inability to detect ^{3}HM in the CSF from CM may be due to the small volume of the injectate plus its limited spread in the SAS.(4) The volume of ^{3}HM was less than 10% of the total spinal CSF volume. Reiselbach (7) showed that in monkeys, the volume of IT injection must approximate 1/10 of the total spinal SF volume for a drug to reach the CM. In a recent study of CSF distribution of morphine, methadone and sucrose following IT injection, Payne et al (6) infused sheep with artificial CSF at a rate 6 times that of endogenous CSF formation. This may not represent the clinical situation. Their findings of recovery of 0.3% morphine in the CSF from CM may be related to this infusion rate. The volume of our injectate was less than 10% of the total spinal CSF volume, and the circulation of CSF in our model was minimally altered.

Conclusions. After IT injection, ^{3}HM spread locally near the injection site in the SC and SR. It continued to spread over the time period observed but the RA decreased with time. The ^{3}HM remained detectable in the SC and SR over the time period described. Under physiological conditions, and with injection volume less than 10% of the total spinal CSF volume, rostral distribution through CSF may be not significant. Renal excretion seemed to be the main route of elimination.

References.

1) Wang JK, Nauss LE, Thomas JE: Pain relief by intrathecally applied morphine in man. Anesthesiology 50: 149-151, 1979.
2) Gustafsson LL, et al: Distribution morphine and meperidine after intrathecal administration in rat and mouse. Anesthesiology 63:483-489,1985.
3) Cousins M, Mather LE: Intrathecal and epidural administration of opioids. Anesthesiology 61: 276-310, 1984.
4) Hylden JLK, Wilcox GL: Intrathecal morphine in mice: a new technique. European Journal of Pharmacology 67: 313-316, 1980.
5) Paterson GMC, McQuay HJ, Bullingham RES, Moore RA: Intradural morphine and diamorphine: dose response studies. Anesthesia 39: 113-117, 1984.
6) Payne R, Inturrisi CE: CSF distribution of morphine, methadone and sucrose after intrathecal injection. Life Science 37: 1137-1144, 1985.
7) Rieselbach RE, DiChiro G, Freireich EG, Rall DP: Subarachnoid distribution of drugs after lumbar injection. N. Engl. J. Med 267: 1273-1278, 1952.



(FIG.1)

Title: COMPARATIVE STUDY OF SUFENTANIL AND ISOFLURANE IN OUTPATIENT SURGERY

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Introduction. Currently there is no available data on the use of sufentanil in short surgical procedures lasting less than 1.5 hours. Sufentanil in small doses of .5 mcg/kg, followed by thiopental, nitrous oxide, oxygen and muscle relaxant gives excellent analgesia and anesthesia for surgical procedures lasting less than 1.5 hours. Clinical experience with this technique suggests that the need for post-operative analgesia is (significantly) less than with isoflurane and hence it may be useful in outpatient surgery, permitting a short recovery time before safe discharge from the hospital. The purpose of the present study is to compare the recovery time following sufentanil, thiopental, nitrous oxide, oxygen and muscle relaxant with that of thiopental, nitrous oxide, oxygen, isoflurane and muscle relaxant sequence in outpatient surgical procedures.

Methods. Informed consent was obtained from 17 unpremedicated ASA I outpatients between the ages of 20 and 40 years, weight 45-85 kg, scheduled for elective laparoscopy procedures.

Each patient was timed when she performed a "star drawing test" with their dominant and non-dominant hand prior to induction of anesthesia. Patients were randomly divided into two groups. Group I had sodium thiopental 4 mg/kg, .5 mcg/kg sufentanil for induction of anesthesia and 1-1.5 mg/kg of succinylcholine to facilitate tracheal intubation. Glycopyrolate .2 mg IV was given prior to injection of succinylcholine. Anesthesia was maintained with nitrous oxide 66% and atracurium as needed for muscle relaxation.

Group II had sodium thiopental 4 mg/kg IV, isoflurane 1-1.5%, glycopyrolate .2 mg IV, succinylcholine 1-1.5 mg/kg for tracheal intubation and atracurium as needed to achieve muscle relaxation. Ventilation was controlled in both groups of patients with tidal volumes of 10-12 cc/kg and rate of 8-10 per minute. End tidal CO_2 in both groups were kept between 32-40 mmHg (measured by mass spectrometry). At the termination of anesthesia both groups received glycopyrolate and edrophonium for reversal of neuromuscular blockade if needed. Recovery from anesthesia was assessed by a nurse upon arrival in the recovery room and timed 30 minutes thereafter according to criteria modified from the standard Aldrete Score:

Consciousness: 1) fully awake, responding on command and oriented to time and place: 2; 2) arousable on calling: 1; 3) not responding: 0.

Respiration: 1) able to breathe deeply and cough freely: 2; 2) dyspnea or slow breathing below eight breaths/min: 1; 3) apnea: 0.

Circulation: 1) blood pressure ± 20 mm of pre-anesthetic level and good color: 2; 2) blood pressure between ± 20-50 mm of mercury or pale or dusky: 1; 3) cyanotic and blood pressure ± 50 of pre-anesthetic level: 0.

Patients were discharged from the recovery room to home when: 1) they had stable vital signs, 2) when oriented to time, place and person, 3) when able to walk unassisted, 4) did not have excessive nausea and vomiting, and 5) performance on the "star drawing test" was the same as prior to anesthesia.

Results. Nine patients received sufentanil (Group I) and eight patients received isoflurane (Group II). Duration of anesthesia was 30 minutes to 80 minutes for Group I and 30 minutes to 90 minutes for Group II. All Group I patients were significantly more awake on arrival in the recovery room. They followed simple commands and were oriented to time and place within 10 minutes of arrival in recovery room. The need for post-operative pain medication was less in Group I compared to Group II. Two out of nine patients in Group I required analgesics for post-operative pain relief, whereas four out of eight patients in Group II required pain relief post-operatively. This difference was statistically insignificant ($p > .2$ Fisher's exact).

The incidence of nausea was almost the same in both groups. Four out of nine patients required medication in Group I and three out of eight required medication for nausea in Group II. ($p > .42$ Fisher's exact).

By the end of 90 minutes there was minimal difference in consciousness and airway scores between the two groups. Group I patients stayed in the hospital an average of 3.28 hours whereas Group II patients remained an average of 3.98 hours. Even though the patients in Group II scored almost the same as in Group I at the end of 90 minutes, the need for more frequent pain medication post-operatively delayed the discharge time in Group II. Post-operative vital signs were stable in both groups. No signs of renarcotization were observed in Group I. Only one patient required naloxone in Group I. No patient had awareness during surgery in any group.

Group	Post-op nausea %	Post-op narcotic %	Post-op stay, min.
I	44.4	22.2	208
II	37.5	50.0	278
STATISTICS	$p > .42$	$p > .2$	

Conclusion. Both agents appear to be suitable for outpatient surgery. Based on the ease of administration, smoothness of the anesthetic course and the uneventfulness of recovery, the sufentanil regimen described here represents a good alternative.

Thanks to R.N. Jamison, Ph.D. for help in design of project.

Title: INHALATION ANESTHESIA DURING HIGH FREQUENCY JET VENTILATION FOR EXTRACORPOREAL SHOCK WAVE THERAPY OF GALLBLADDER STONES

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Introduction. Animal experiments confirmed the effectiveness of extracorporeal shock wave lithotripsy (ESWL) for the disintegration of gallstones (1). However, they also demonstrated hemorrhage of the basal pulmonary segments (in the vicinity of the shock wave axis). The specific circumstances of cholelithotripsy in humans include (2): 1. Positioning of the patient in the water bath in prone position. 2. Modified shock wave characteristics (lower energy level, reduced focus area requiring more accurate targeting). 3. Continuous sonographic stone localisation. The objective of this study was to test a method of anesthesia suitable for gallstone-lithotripsy, which might render the administration of opiates unnecessary (spasm of the biliary tract sphincter !).

Methods. With prior approval of the institutional review board 15 informed patients (3 male, 12 female/age 42 yr (median value), range 27-63/ ASA-status I-III) were immersed under general anesthesia (induction with thiopental, maintenance with $N_2O:O_2=1:1$, enflurane, relaxation with vecuronium) into the tub of the lithotripter (FIG.1). Prior to shock wave application, we switched from conventional mechanical ventilation (CMV/ventilatory rate 10/min) to high frequency jet ventilation (HFJV/ventilatory frequency 100/min, inspiratory time 20%). By integrating a sliding venturi device (Bird) (3), the entrainment volume was sufficient to control the depth of anesthesia with the entrainment-gas mixture ($N_2O:O_2=1:1$, enflurane) from the conventional ventilator (FIG.2). The use of a triple lumen endotracheal tube permitted continuous monitoring of the tracheal gas mixture (pCO_2, $\%O_2$, $\%N_2O$, %enflurane) and of the pressure levels in the trachea. Measurements of endtidal concentration of enflurane (C_{et}enfl.) and endtidal pCO_2 ($P_{et}CO_2$) was obtained by turning off the HFJ-ventilator (Acutronic MK 800) and providing 3-5 tidal volume breaths from the conventional ventilator (Servo 900 B). Data were analyzed by Wilcoxon's matched pairs test with $p<0,01$ being considered significant.

Results. Under CMV the peak inflation pressure (PIP) was measured at $10 cmH_2O$ (7-18). Stone motion due to ventilation was 20mm (10-45). During HFJV stone movement (3 mm (3-5)) as well as PIP (7 cm H_2O (5-14)) were reduced significantly. PaO_2 or $PaCO_2$ values did not differ significantly between the two methods of ventilation (TABLE 1). In no case was additional injection of opiates necessary. Organ lesions could not be seen (checked by CT, sonography, cholecystography, chest x-ray).

Discussion. 1. With HFJV respiratory stone motion can be minimized. In patients with normal pulmonary function, HFJV does not present an additional risk even in the prone position. 2. The described procedure permits anesthetic management with only volatile anesthetics during CMV and HFJV. 3. We could provide a sufficient distance between the base of the lung and the penetrating shock waves.
This method of anesthesia enhances precision of shock wave application and effectiveness of ESWL-therapy of gallbladder stones.

References.

1. Brendel W, Enders G. Shock waves for gallstones: animal studies. Lancet 1983; 1:1054
2. Sauerbruch T, Delius M, Paumgartner G, Holl J, Wess C, Weber W, Hepp W, Brendel W. Fragmentation of gallstones by extracorporeal shock waves. N Engl J Med 1986; 314: 818-22
3. Gallagher RC, Banner MJ, Modell JH. Comparison of delivery systems for high frequency jet ventilation. Crit Care Med 1985; 13:313

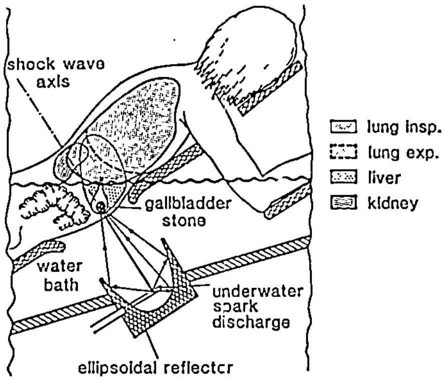

FIG.1 Positioning of patient in the lithotripter bath. Sagittal section at the level of the gallbladder.

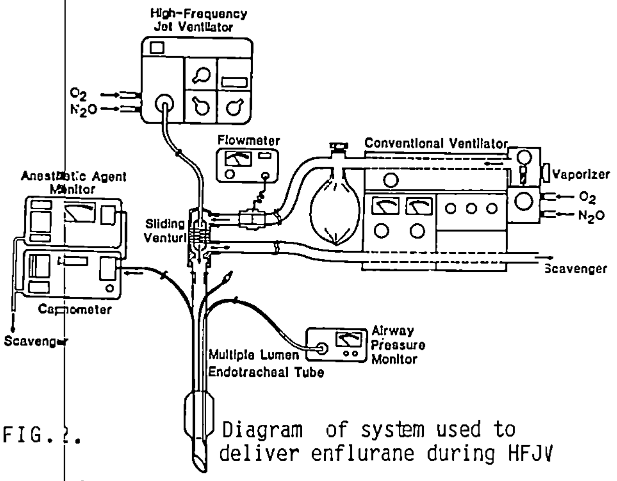

FIG. 2. Diagram of system used to deliver enflurane during HFJV

$F_IO_2=0,5$			n=15	
		range	median	
P_aO_2 (mm Hg)	CMV	162 - 281	242	
	HFJV	151 - 293	239	n.s.
P_aCO_2 (mm Hg)	CMV	30 - 39	35	
	HFJV	31 - 43	36	n.s.
$P_{et}CO_2$ (mm Hg)	CMV	26 - 41	37	
	HFJV	29 - 45	40	
C_I Enflurane (Vol %)	CMV	0,6 - 1,1	0,6	
	HFJV (Entr.)	1,2 - 2,5	1,7	
C_{et}Enflurane (Vol %)	CMV	0,4 - 0,95	0,45	
	HFJV	0,4 - 1,05	0,55	n.s.

n.s.=no significant difference CMV vs. HFJV

TABLE 1. Parameters of gas exchange during CMV and HFJV

Title: SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND NON-THORACIC OPERATIONS: INCIDENCE OF POSTOPERATIVE PULMONARY COMPLICATIONS

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PURPOSE. Many authors have studied the risk of postoperative pulmonary complications (PPC) in patients with chronic obstructive pulmonary disease (COPD) undergoing thoracic operations. Less is known about the risk of PPC in patients undergoing non-thoracic operations. We report the incidence of PPC in a group of patients with severe COPD (FEV1 less than 1.2l). In addition, we have examined other risk factors for PPC (1) and prospectively applied Shapiro's scoring system (2) which categorizes patient risk for PPC.

METHOD. During a 9 month period, every patient with an FEV1 less than 1.2l who underwent surgery was studied. Values for preoperative risk factors were obtained: age, smoking history, sputum production, preoperative pulmonary preparation, incentive spirometry, weight, and room air blood gas. ASA and Shapiro scores were recorded. Intraoperative risk factors such as type of anesthesia, length of anesthesia, length of surgery, incision site, and operative procedure were also recorded. The attending anesthesiologist chose the anesthetic techniques. Postoperative complications, defined as postoperative ventilatory failure, pneumonia, refractory bronchospasm, prolonged ICU stay (longer than 3 days), and mortality were noted. PPC frequencies were compared by Fisher exact test.

RESULTS. Twenty-one patients were studied. Important risk factors are presented in Table I. The average Shapiro score was 3.5. Fifteen patients (71%) went to the ICU postoperatively. Three patients (15%) had postoperative pneumonia with leukocytosis, fever, and sputum cultures. Seven patients (33%) were not extubatable at the end of surgery. One patient had refractory postoperative bronchospasm and one patient died. Eight of 11 (73%) patients with abdominal incisions had a PPC and only one of ten patients (10%) with a nonabdominal operation had a PPC. This difference was statistically significant by Fisher's exact test ($P < .01$). There was no statistically significant difference between the type of anesthetic and PPC.

DISCUSSION. Patients with severe COPD may undergo nonthoracic operations with great morbidity, as evidenced by ICU stay and postoperative ventilator dependence. Shapiro has stated that if the sum of %FEV1/FVC and %FVC is less than 100, there is a 50% chance of acute ventilatory failure in the first 24 hours. This finding alone translates into a Shapiro risk score of 2. All of our patients had a score of 2 or more. In our study, six of eight patients (75%) who received general anesthesia for abdominal procedures required postoperative ventilatory support; four remained intubated more than 36 hours postoperatively, one required reintubation, two became chronically ventilator dependent, and one died. Three patients received regional anesthesia for abdominal operations and all developed a PPC: two had to be intubated within 48 hours postoperatively (one of whom became ventilator dependent and died); and the third developed pneumonia. Of six patients who underwent TUR procedures only one went to the ICU postoperatively and none had a PPC. Four of these patients received regional anesthesia and two received general anesthesia.

The surgical incision site is more important in determining the incidence of PPC than the type of anesthetic.

TABLE I

Risk Factors

PT	AGE	ASA	SHAP	FEV1	ANES*	INCIS**	COMP***
1	68	4	5	0.61	2	0	
2	74	3	3	0.86	2	0	
3	51	3	3	0.77	2	0	
4	62	3	2	1.02	2	0	
5	82	4E	2	0.75	2	4	2
6	70	4	3	1.00	2	5	3
7	56	4E	4	0.70	2	5	2,5
8	93	3	4	0.80	3	0	
9	64	4	4	0.65	4	0	
10	55	3	3	1.10	4	0	
11	65	3	3	1.02	4	0	
12	75	3	4	0.75	4	0	1
13	63	4	4	0.57	4	3	1,3
14	58	4	4	0.70	4	4	1
15	65	4E	5	0.70	4	4	1,4
16	59	4E	2	1.20	4	5	1,3
17	63	4E	4	0.85	4	5	1
18	69	4	4	0.80	4	5	
19	66	3	4	1.05	4	5	
20	59	3	3	1.13	4	5	1
21	67	3	3	1.07	2,4	0	

* Anesthetic: 2 = regional, 3 = GA mask, 4 = GA Ett

** Incision: 0 = TUR, head and neck, or extremity, 3 = upper abdomen transverse, 4 = upper abdomen vertical, 5 = lower abdomen

*** Complication: 1 = unable to be extubated postop, 2 = intubated postop, 3 = pneumonia, 4 = refractory bronchospasm, 5 = died

REFERENCES.

1. Tisi GM: Preoperative Evluation of Pulmonary Function. Am Rev Resp Dis 119:293-310, 1979.
2. Shapiro BA: Evaluation of Respiration Function in the Perioperative Period, ASA Refresher Course Lecture: 222, 1-7, 1979.

Title: NONINVASIVE PREOPERATIVE CARDIOVASCULAR ASSESSMENT AND INTRAOPERATIVE HYPOTENSION

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INTRODUCTION. Careful preoperative history and physical exam may not indicate that a patient is at increased risk for perioperative hemodynamic instability. Particularly in the sedentary patient, previously unsuspected cardiac disease or relative hypovolemia can contribute to perioperative cardiovascular complications. Del Guercio (1) inserted pulmonary artery catheters in 148 elderly patients, otherwise cleared for surgery, and found that 23% had markedly abnormal hemodynamic parameters. Routine preoperative pulmonary artery (PA) catheterization in elderly patients is not done at our institution because it is not without risk. However, recently available, noninvasive devices capable of measuring cardiac output, oxygenation, and skin oxygen delivery may provide additional information about the patient's hemodynamic status. We used a collection of these devices to noninvasively measure preoperative cardic output, heart rate (HR), mean arterial pressure (MAP), transcutaneous oxygen tension (TcO2), and arterial oxygen saturation (SaO2). We then observed each patient for any episodes of intraoperative hypotension.

METHODS. This study was approved by the institutional review board. Patients undergoing elective operations, and in whom pulmonary artery catheterization was not planned, were eligible for study entry. Upon entering the preoperative holding room, each patient had a Novametrix 807 transcutaneous PO2 probe, an Ohmeda 3700 finger pulse oximeter probe, electrodes for a Bomed NCCOM 3 thoracic bioimpedance monitor and a Bard Sentron noninvasive blood pressure monitor placed. All probes and monitors were applied and calibrated according to the manufacturer's recommendations. The transcutaneous probe was calibratec before each patient and allowed to warm up to 44°C for 15 minutes before any measurements were mace. Each variable was measured at least five times in each patient (usually at 1 minute intervals) and the average value used. Cardiac index (C.I.) was calculated by dividing measured cardiac output by calculated body surface area. The patients were also rated by ASA classification and the cardiac risk index proposed by Goldman (2). The patient's anesthesiologist was blind to the study measurements. Intraoperative hypotension was defined as any blood pressure 20% or more below the patient's baseline before the skin incision that required drug treatment.

RESULTS. Eighty-nine patients, aged 43 to 92 were studied. Sixty patients were aged 65 or older. HR ranged between 40 - 104. MAP ranged between 68 - 126 mmHg, SaO2 was greater than 89% in all patients, TcO2 on room air ranged between 28 - 76 mmHg, and C.I. ranged between 1.6 - 5.57 l/min/m2. Nineteen patients (21%) had an episode of intraoperative hypotension severe enough to require drug therapy. No patient suffered a perioperative myocardial infarction or died. Five of 35 patients (14%) rated ASA I had a hypotensive episode. Thirteen of 51 patients (25%) rated ASA II had a hypotensive episode. One of three patients (33%) rated ASA IV had a hypotensive episode. Twelve of 77 patients (15.6%) with C.I. between 2.0 - 4.0 l/min/m2 had an hypotensive episode. Of 12 patients whose C.I. was outside this range, seven (48%) had an intraoperative hypotensive episode. The difference between these two groups was statistically significant by Chi Square analysis without Yates Correction factor (P 0.001). Using C.I. as a diagnostic test to predict which patients would have a hypotensive episode has a positive accuracy of 58.3%, sensitivity of 36.8%, and a specificity of 92.8%.

DISCUSSION. Patients with low C.I. may be at increased risk for hypotensive episodes because of relative hypovolemia or decreased contractility. Patients with high C.I. may be in a hyperdynamic state in response to some physiologic stress. When anesthesia is induced in these patients perhaps this compensatory response is blunted, vascular tone is lost, and the patients become relatively hypovolemic. Anesthesiologists preoperatively evaluating elderly, poorly communicative and bedridden patients may find themselves guessing about their patient's real cardiovascular status. Del Guercio and Cohn (1) have shown that invasive monitoring can improve outcome in a high risk patient subgroup. They found that 34 of their 148 (23%) study patients had previously unsuspected, severe hemodynamic derangements. Because of their assessment, 26 of these patients underwent smaller procedures or were postponed. Eight patients underwent general anesthesia and all died. Although preoperative PA catheterization may be justified in elderly patients with significant cardiac histories, it probably is not justified solely on the basis of advanced age and an unobtainable cardiovascular history. In these patients noninvasive assessment of cardiovascular parameters provides a reasonable alternative to invasive monitoring.

Noninvasive preoperative cardiac output determination can identify a patient subgroup at increased risk for intraoperative hypotension. Since noninvasive devices pose minimal patient risk, noninvasive preoperative cardiovascular assessment may be desirable, particularly if this information can be used to prevent not only intraoperatively hypotension but also related cardiovascular complications.

REFERENCES.

1. Del Guercio LRM, Cohn JD. Monitoring Operative Risk in the Elderly. JAMA 1980:243:1350-5.
2. Goldman L, Caldera DL,Nussbaum SR, et al: Multifactorial Index of Cardiac Risk in Noncardiac Surgical Procedures. N Engl J Med 1977;297:845-50.

Title: A NATIONAL SURVEY OF ANESTHETIC COMPLICATIONS IN CHILDREN WITH DUCHENNE'S MUSCULAR DYSTROPHY

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Introduction. Numerous anecdotal reports have described anesthetic complications in patients with Duchenne's Muscular Dystrophy (DMD).[1] Many of the described events have resembled malignant hyperthermia (MH)[2] but the exact relationship of these anesthetic reactions to MH remains controversial.[3] The magnitude of the risk is unknown. To provide more data on the anesthetic experience of DMD children, we undertook a survey of all Muscular Dystrophy Association (MDA) clinics in the U.S.

Methods. Questionnaires were sent to all MDA clinic directors (most were neurologists). Information requested included: (1) Number of patients followed; (2) Anesthetic technique(s) currently used to obtain diagnostic muscle biopsies in suspected DMD; (3) Major complications which had occurred during biopsies; (4) Knowledge of unreported major anesthetic complications occurring during other surgeries in DMD patients. A major complication was considered to be an event which included all or some of the following: rigidity, major cardiac arrythmias, hyperkalemia, fever, elevated CPK, pigmenturia, cardiac arrest. Further information was obtained when possible by follow-up call to those answering "yes" to #4. Type of anesthesia used was determined in most cases but in some this data was unavailable (listed as "unknown").

Results.

A. Response

All 234 MDA clinics identified in the MDA program guide were contacted and 147 responded (63%). 108 of these clinics do biopsies for DMD. The maximum number of DMD children covered by this survey were calculated using the demographic data from question #1; this total was just under 7000.

B. Anesthesia for Biopsies

There was a marked preference for local anesthesia to do muscle biopsies: 75% of centers use this technique exclusively. Other techniques used are listed in table 1.

C. Complications

Numbers of complications with the features mentioned above which occurred during muscle biopsy are listed in table 2. None occurred during local anesthesia. 4/6 occurred during halothane anesthesia. One of these occurred in the absence of succinylcholine (SCh). Table 2 also lists the numbers of such complications reported which occurred during other surgeries: A total of 30 major complications was reported. Again, halothane and SCh predominate as the known agents used in these cases.

Discussion. There is evidence in the literature to suggest that children with DMD are susceptible to particular complications following general anesthesia with halothane or SCh. The reported reactions have included combinations of: rigidity, arrythmias, fever, hyperkalemia, pigmenturia, CPK elevation and cardiac arrest. Some investigators have identified these reactions as MH[2] while others postulated a distinct entity labeled the "DMD anesthetic reaction"[3]. There are theoretical resons for the muscle in DMD and that in MH to share similar susceptibilities to volatile anesthetics and SCh.[3] We sought evidence of previously unreported anesthetic complications in DMD by means of a survey directed to those doing primary children care for these patients and found evidence of 36 reactions with the features mentioned above. A numerical anesthetic risk for DMD children cannot be calculated from this data as the number of anesthetics given is not known. However, there were 36 children who suffered a major anesthetic reaction in a group of DMD patients which numbers at most 7000. The prevelance of risk for such a reaction is thus more than 1 in 200. Where anesthetic agents could be identified, the vast majority of reactions followed halothane and SCh.

Conclusions.

1. No complications were reported during local anesthesia which is the preferred technique for diagnostic muscle biopsy at most DMD clinics.

2. Our study supports the anecdotal (and theoretical) data that children with DMD are susceptible to major anesthetic reactions which are often associated with the administration of halothane and SCh. The relationship of these reactions to classical MH remains to be defined.

References.

1. Brownell AKW, et.al. Malignant Hyperthermia in Duchenne Muscular Dystrophy. Anesthesiology 58: 180-181, 1983.
2. Rosenberg H, Heiman-Patterson T. Duchenne's Muscular Dystrophy and Malignant Hyperthermia: Another Warning. Anesthesiology 59:362, 1983.
3. Wilner J. et.al. Drug-induced fiber necrosis in Duchenne Dystrophy. Ital J Neurol Sci (supp) 3:117-121, 1984.

Table 1. Anesthetic Technique used for Diagnostic Muscle Biopsy:

Technique	# of Centers	% of Total
Local	81	75.0%
Halothane + SCh	1	0.9%
Halothane - SCh	3	2.7%
GA without Halothane or SCh	10	9.3%
More than one technique	13	12.0%

Table 2. Complications During Surgery

Anes. Techniques	Muscle Biopsy	Other
Local	0	0
Halothane + SCh	3	17
Halothane - SCh	1	1
Ga without Halothane or SCh	0	1
Unknown	2	11
Total	6	30

Title: A COMPARISON OF INDUCTION AND MAINTENANCE OF ANESTHESIA WITH PROPOFOL TO INDUCTION WITH THIOPENTAL AND MAINTENANCE WITH ISOFLURANE

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Purpose: This study was done to compare induction and maintenance of anesthesia with propofol to induction with thiopental and maintenance with isoflurane for short surgical procedures ($<$ 2 hours).

Methods: This study was approved by the Committee for Human Investigation and written informed consent was obtained. ASA I or II patients, ages 18-65 years, were divided by random assignment into two groups of thirty each (N=60). Patients were premedicated with atropine 0.4 mg administered intramuscularly. One minute prior to induction of anesthesia all patients received d-tubocurarine 3 mg and fentanyl 1.5 mcg/kg intravenously and oxygen was administered by face mask. Anesthesia was induced with propofol 2.5 mg/kg (Group I) or thiopental sodium 5 mg/kg (Group II) administered over 20-30 seconds. Tracheal intubation was facilitated with 1.5 mg/kg succinylcholine administered intravenously three minutes after beginning induction. Anesthesia was maintained with intermittent boluses of propofol 0.625 mg/kg and 60-70% nitrous oxide in oxygen and with 0.2-2.0% end-tidal isoflurane and 60-70% nitrous oxide in oxygen in Groups I and II respectively. When indicated a 0.2% succinylcholine drip was administered in both groups to provide muscle relaxation. Blood pressure, pulse and respiratory rates were recorded one minute before and after the administration of d-tubocurarine and fentanyl and each minute for three minutes after injection of the induction agent and then at five minute intervals for the duration of the anesthetic. The cessation of counting (induction time) was recorded as the number of seconds from the beginning of injection of the induction agent. If induction of anesthesia was not accomplished within one minute, a second dose of the induction agent (1/4 the original dose) was administered. At the end of surgery, time to return of response to verbal commands and orientation were recorded in minutes from discontinuance of nitrous oxide. Results are reported as the mean ± SEM. Statistical significance was accepted when $p < 0.05$.

Results: There were no significant differences between the groups with respect to ASA status, race, age, sex, weight, smoking history, incidence of apnea or quality of induction. Induction times were 38.2 ± 1.44 seconds in Group II and 42.0 ± 1.18 in Group I with P = 0.04. Both thiopental and propofol produced a significant increase in heart rate at one minute following induction (AI). When compared to baseline, systolic and diastolic blood pressures were significantly decreased at three minutes following induction and prior to incision (PI) in both groups. Systolic blood pressure was also significantly decreased at the termination of anesthesia (TA) in Group II. Diastolic blood pressure significantly increased AI when compared to PI values in both groups. (See Table I) Times to response to verbal commands and orientation were 3.3 ± 0.6 minutes and 6.5 ± 1.4 minutes respectively in Group I and 7.5 ± 0.9 minutes and 15.9 ± 2.5 minutes respectively in Group II. Both times were significantly shorter in Group I. Anesthesia was successfully maintained with propofol and nitrous oxide in oxygen in all Group I patients. The average total dose of propofol was 0.130 ± 0.010 mg/kg/min. Use of a muscle relaxant was necessary in Group I to prevent patient movement during the surgical procedure. The average mean end-tidal isoflurane concentration ranged from 0.53 ± 0.05% to 0.67 ± 0.07% during the surgical procedures. The average duration of surgery in Group I was 61.0 ± 6.0 minutes and 56.3 ± 5.2 minutes in Group II. Five Group I patients complained of pain on injection, one required atropine to treat bradycardia intraoperatively and another required ephedrine to treat mild hypotension. Seven patients in Group I experienced excitement in the recovery room as did six in Group II. No cases of phlebitis or allergic reaction were noted.

Discussion: Propofol appears to be a suitable anesthetic agent for induction and maintenance of anesthesia for short surgical procedures.(1) In this study hemodynamic responses observed were similar to those seen in patients in whom anesthesia was induced with thiopental and maintained with isoflurane. Emergence from anesthesia was significantly faster in patients anesthetized with propofol when compared to patients anesthetized with isoflurane.

TABLE I

Parameter	Group I (N=30)	Group II (N=30)
Heart rate (bpm)		
basal	81.1 ± 3.6	80.0 ± 3.7
1 min	#* 89.1 ± 4.1	#* 90.9 ± 2.6
3 min	#* 73.1 ± 4.1	* 80.2 ± 2.4
Prior incision	# 73.0 ± 3.7	80.4 ± 3.7
After incision	# 78.9 ± 3.2	#* 88.8 ± 4.0
End anesthesia	# 72.2 ± 2.9	+ 85.4 ± 3.9
Systolic BP (torr)		
basal	136.9 ± 3.0	137.4 ± 2.5
1 min	135.9 ± 2.5	133.7 ± 3.0
3 min	#* 116.1 ± 3.2	#* 125.5 ± 2.4
Prior incision	# 122.4 ± 2.9	+ # 115.2 ± 2.9
After incision	* 131.6 ± 2.7	#* 130.8 ± 3.2
End anesthesia	129.9 ± 3.0	# 127.9 ± 3.2
Diastolic BP (torr)		
basal	77.1 ± 2.2	77.9 ± 1.7
1 min	76.0 ± 2.8	76.3 ± 2.1
3 min	#* 60.1 ± 2.8	# 71.5 ± 2.5
Prior incision	# 65.8 ± 3.1	# 64.6 ± 3.3
After incision	* 79.3 ± 2.8	* 76.5 ± 2.3
End anesthesia	79.2 ± 3.1	* 75.6 ± 2.7

N=60

* = $p < 0.05$ when compared to preceding value
# = $p < 0.05$ when compared to basal reading
+ = $p < 0.05$ when propofol values compared to thiopental values

Reference

1) Briggs LP, Clarke RSJ, Dundee JW, et al: Use of di-isopropyl phenol as main agent for short procedures. Br J Anaesth 53(11):1197-1202 Nov 1981

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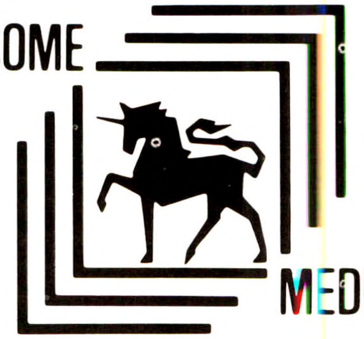

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